Arboviral Diseases

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UNCLASSIFIED

Lecture Objectives

- Increase knowledge of:
  - Arbovirology
  - Epidemiology of tropical viral disease threats
  - Select diseases clinical presentation
  - Key points related to prevention and treatment

Threat Assessment – ID Risk

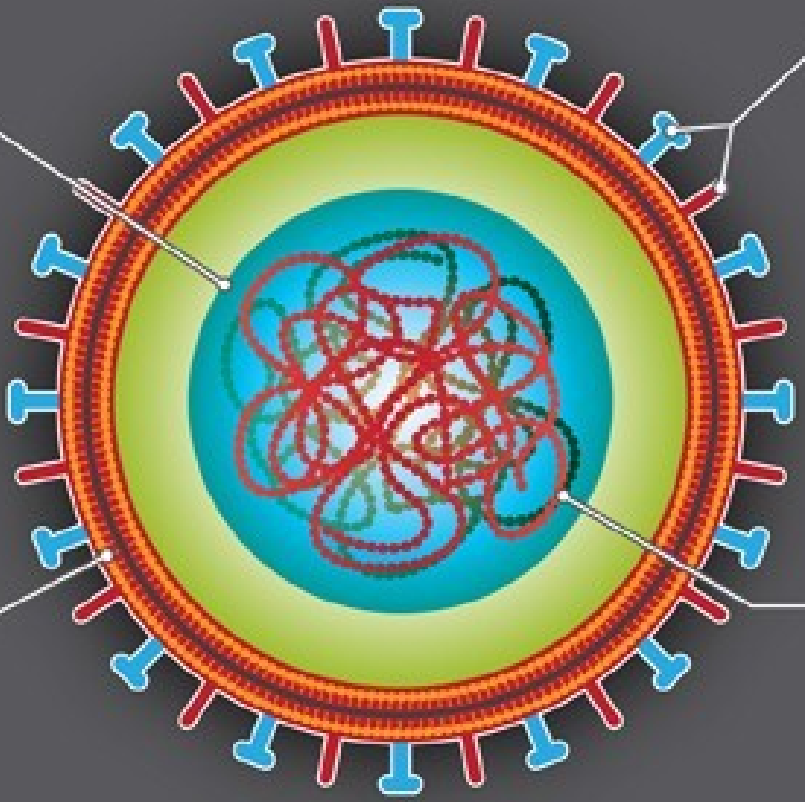
Disease	2010 COCOM panel	ID-IDEAL
Malaria	1	2
Dengue	2	3
Diarrhea, bacterial	3	1
MDR wound pathogens	4	NA
Leishmaniasis	5	19
Q fever (Coxiella burnetti)	6	26
Norovirus / viral diarrhea	7	NA
Influenza	8	NA
Leptospirosis	10	7
Diarrhea, protozoal	11	11
TB	12	NA
CCHF	13	10
HIV	14	8
HFRS	15	17
Chikungunya	16	4
Meningococcal meningitis	17	20
Plague	18	27
Ricketsioses	19	18
Viral encephalitides	20	NA

What is a virus?

- Defined: A sub-cellular agent consisting of a **core of nucleic acid** surrounded by a **protein coat** that must use the **metabolic machinery of a living host to replicate** and produce more viral particles.

- Viruses are known to infect almost all organisms, including bacteria, fungi, plants, insects, and vertebrates.
- 20-300 nm in diameter; a “filterable” agent.

VIRUS STRUCTURE



Capsid
The capsid contains the virus' genetic material (DNA or RNA)

Surface proteins
These help the virus recognise and bind to cells in the host organism

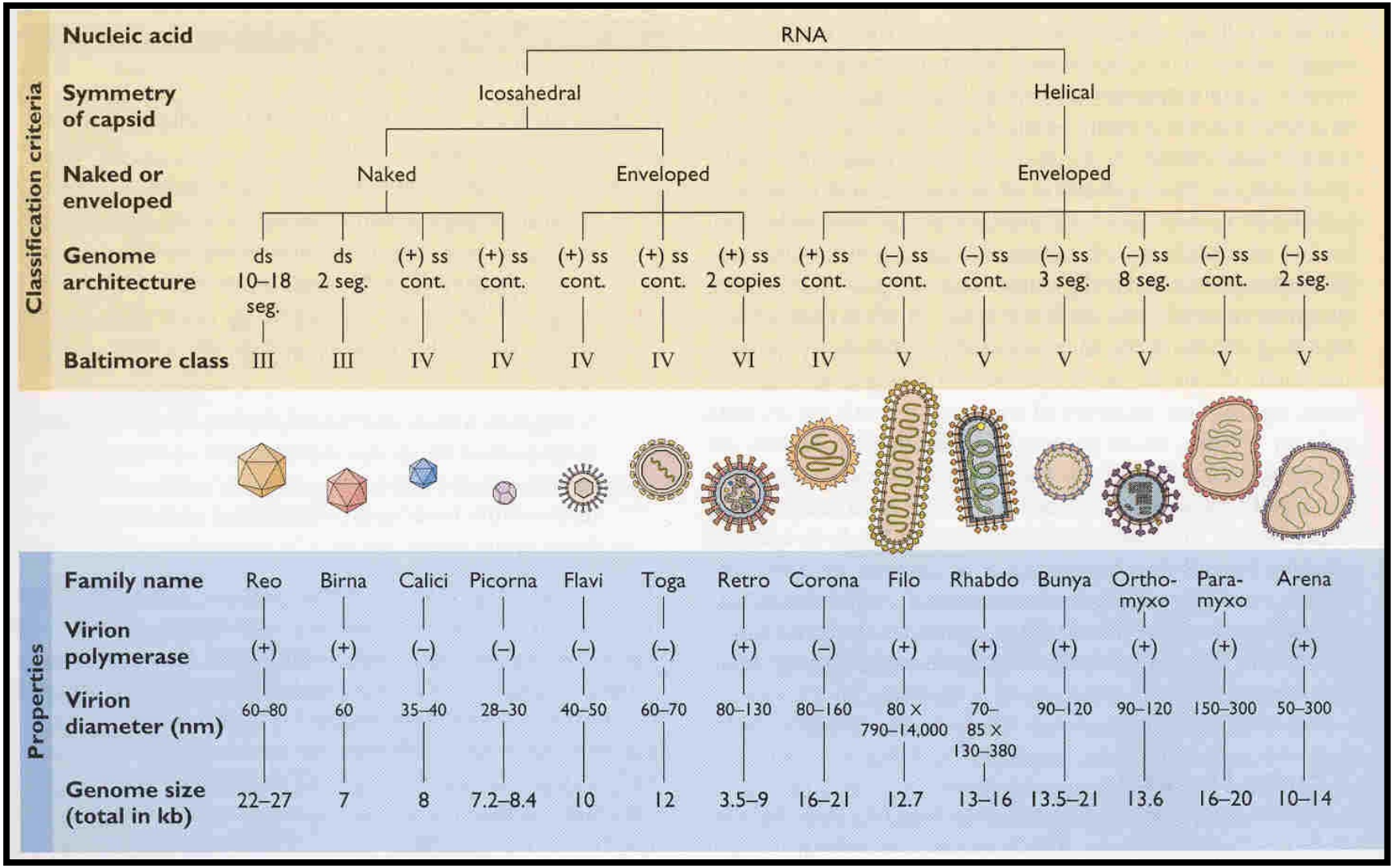
Viral envelope
The viral envelope is made from fatty lipid molecules taken from cells in the host

Virus genetic material
(DNA or RNA)
The virus' genetic material contains the instructions for making new copies of the virus

How do they classify viruses?

- Basic criteria used to classify viruses
  - Nature of the **nucleic acid** in the virion
  - Symmetry of the **capsid**
  - Presence or absence of an **envelope**
  - **Dimensions** of the virion and capsid

Classification Scheme



Source: Flint et al. 2000. *Principles of virology*

Classification Scheme

Classification

Nucleic acid----------

Symmetry of capsid-------

Naked or enveloped------

Genome architecture----

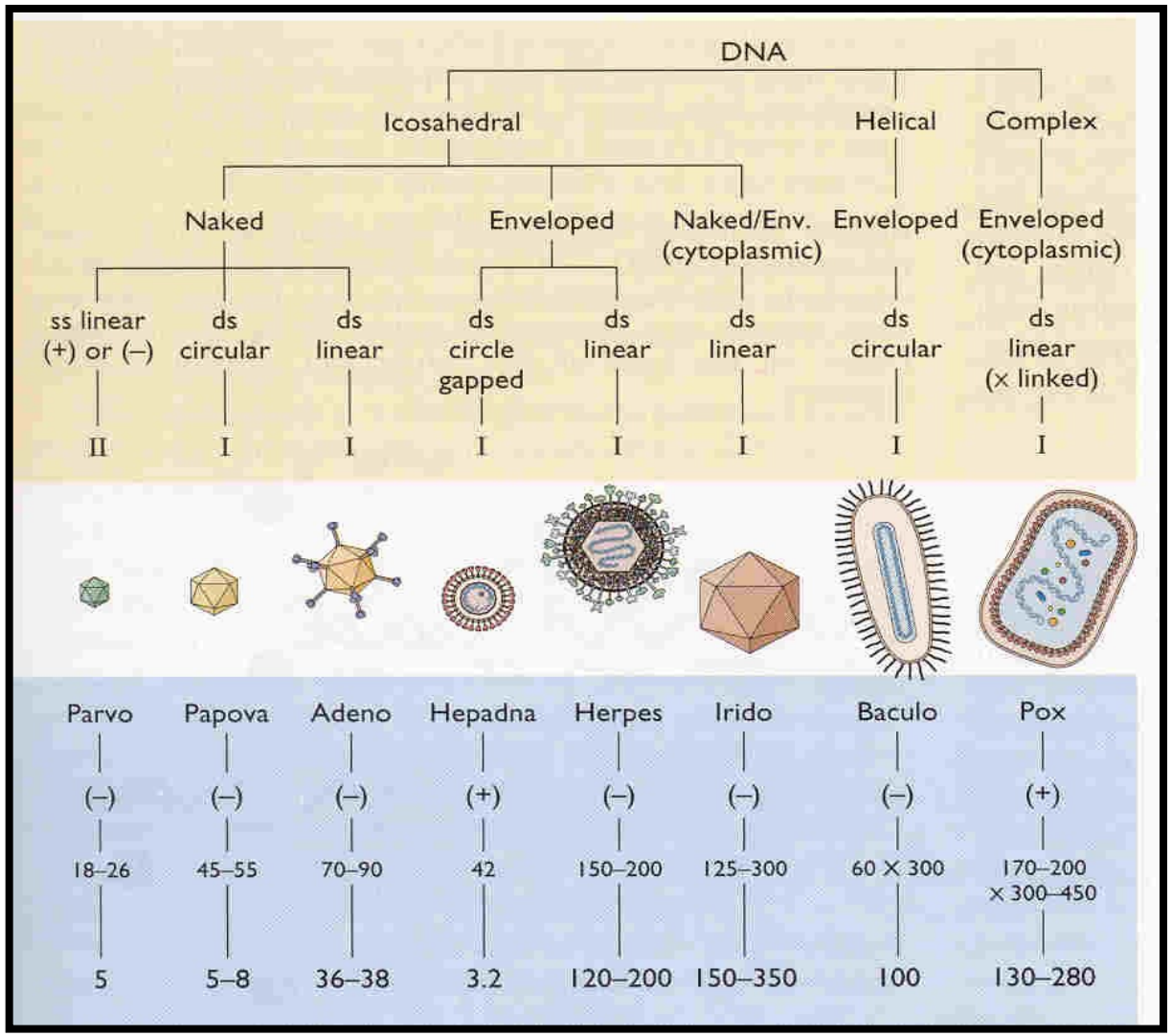
Baltimore class----------

Properties criteria

Family name----------

Virion polymerase--------

Virion diam

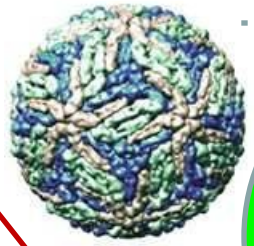


Source: Flint et al. 2000. *Principles of virology*

What is an arbovirus?

- Defined: Arthropod-borne viruses (arboviruses) are **transmitted biologically among vertebrate hosts by hematophagous (blood feeding) arthropod vectors** such as mosquitoes and other biting flies, and ticks.

Arboviral Transmission Dynamics



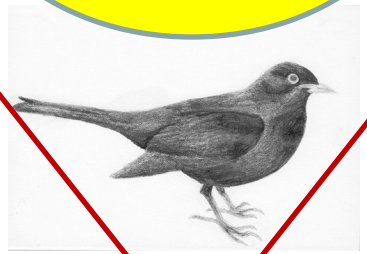
Virus

Vector

Ecology

Host Reservoir

Ecology



Accidental Hosts

Transmission Cycle Example - WNV

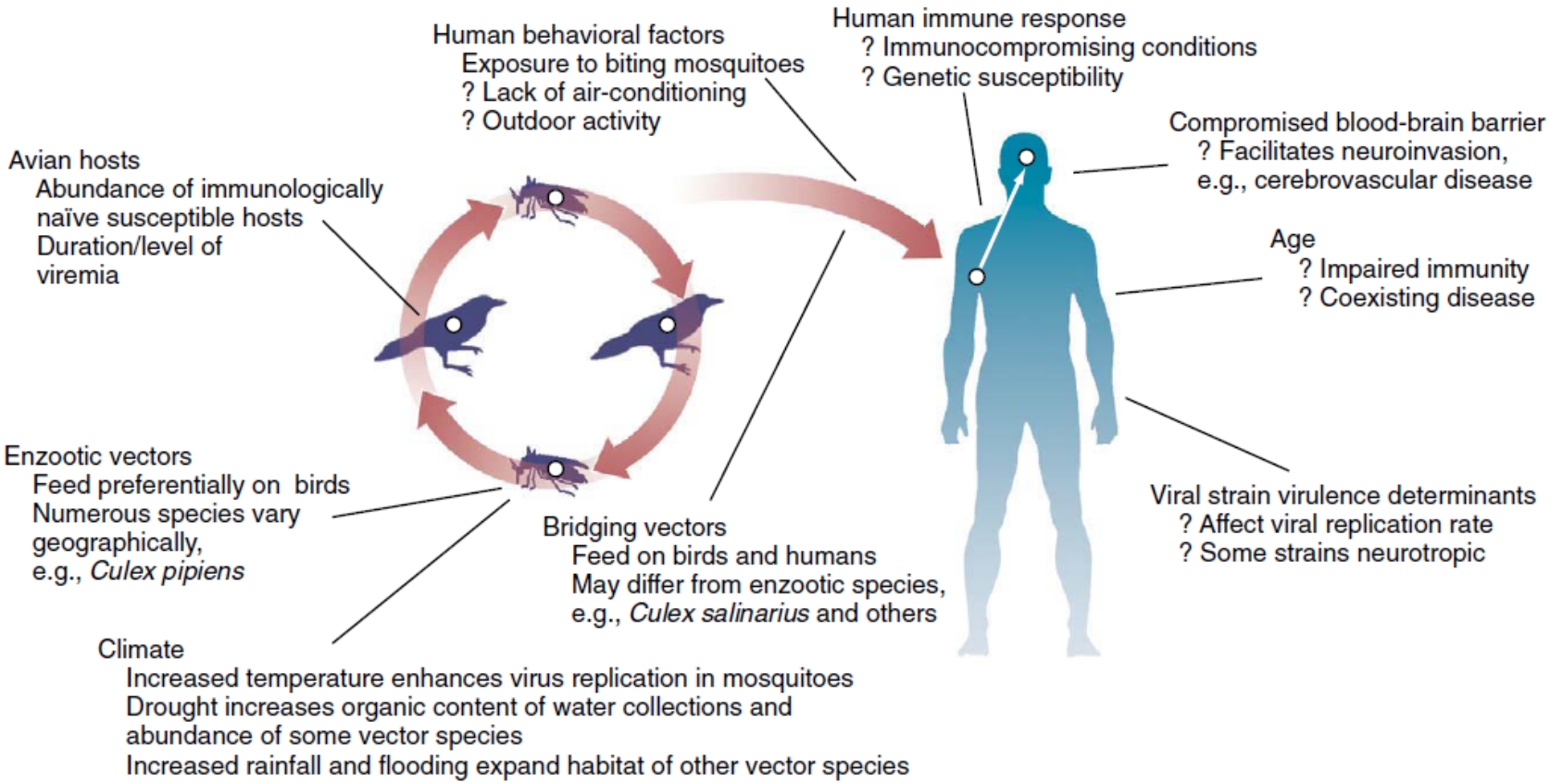


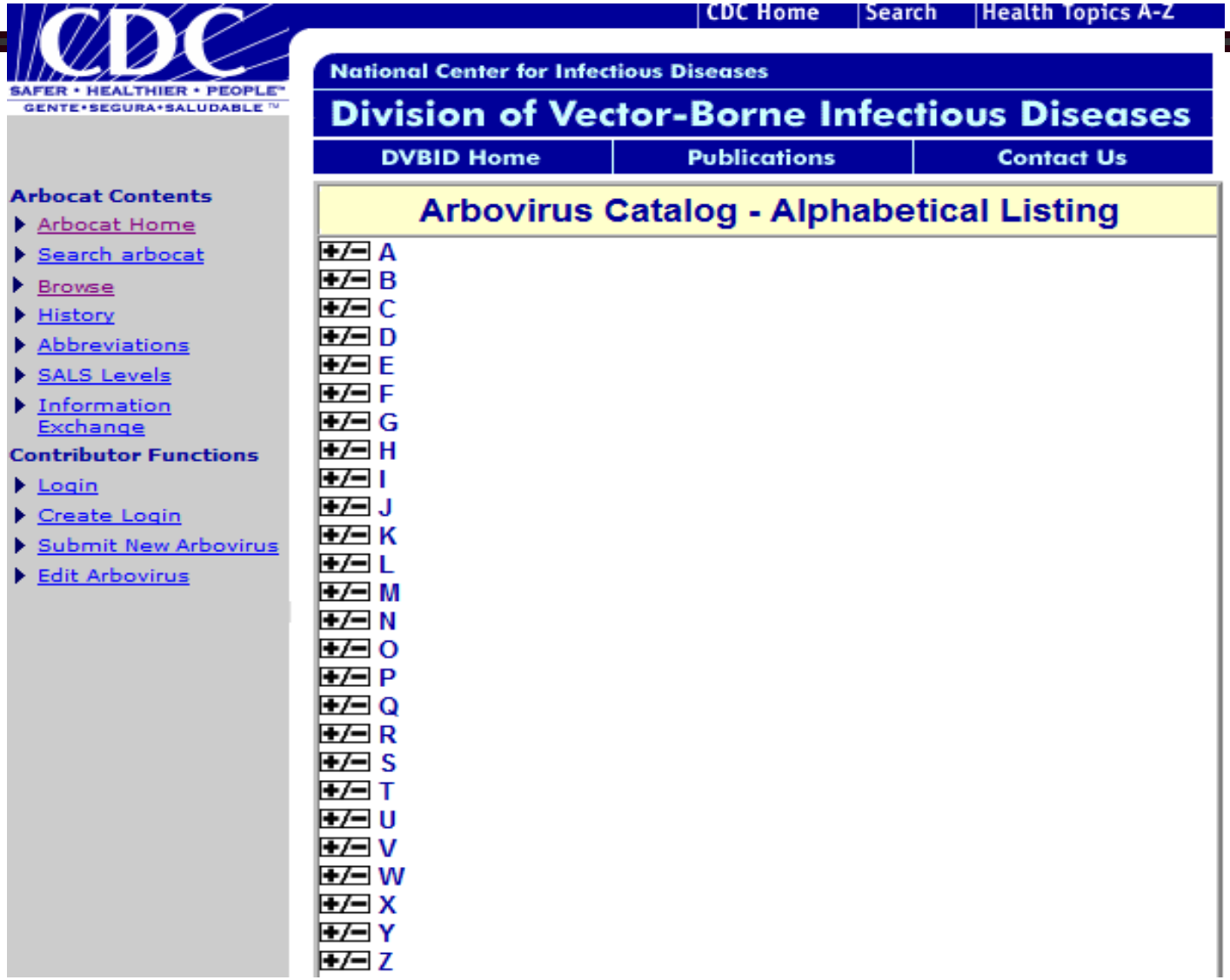
Figure 153-3 West Nile virus transmission cycle and examples of modifying climatologic, vertebrate, mosquito, and human factors on infection and illness.

What makes a good arbovirus reservoir?

- The host is **present** in large numbers and is readily **accessible** to vectors in time and space.
- The host is **attractive** to arthropod vectors and allows vectors to feed upon it.
- The host is **susceptible** to virus infection, experiences low mortality from infection, and **becomes viremic** with a titer of sufficient magnitude and duration to infect susceptible blood-feeding vectors.
- The life history of the host proceeds in such a way that immunologically susceptible individuals **enter the population** at times of active transmission.
- Host **herd immunity remains low**

Arboviruses

- Occur in nearly all parts of the world except the ice caps
- Over 500 distinct viruses, ~100 causing human infections
- Nearly all arboviruses included in 5 families:
  - Flaviviridae
  - Togaviridae
  - Bunyaviridae
  - Reoviridae
  - Rhabdoviridae



http://wwwn.cdc.gov/arbocat/

Be a virus, see the world.

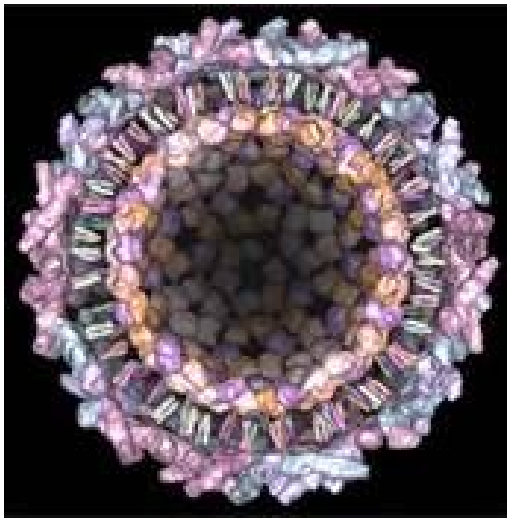
Question

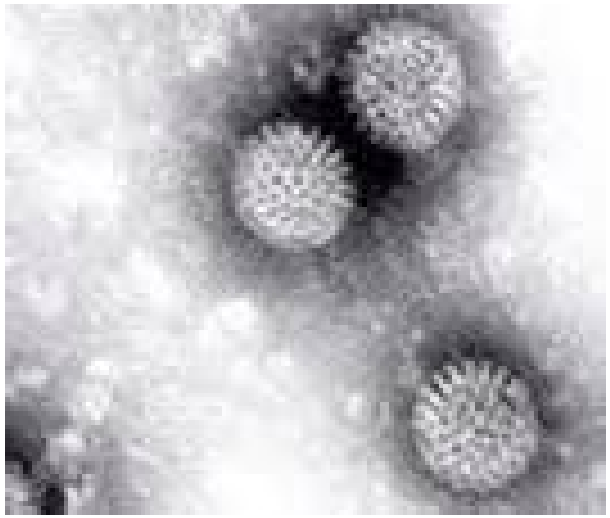
- 32 yo WM presents with complaints of joint pain and severe fatigue 5 days after returning from a vacation in Northeastern Australia. Although he slept indoors, tourist activities were predominantly outdoors. He had no fresh water exposure. Food and beverages were prepared by the hotel and tourism company. He had no animal exposures.
  He is ill appearing and uncomfortable. VS, including temperature, are normal. On exam he has symmetrical tenderness and warmth in his ankle and knee joints, there is a L knee effusion. He has a faint macularpapular, non-pruritic rash on his trunk.

- What infection would be #1 on your differential diagnosis?
  A. Leptospirosis
  B. Malaria
  C. Chikungunya
  D. Dengue
  E. Ross River virus

Arboviruses

- Family Togaviridae
  - Genus Alphavirus (30 species, examples below)
    - Barmah Forest, Chikungunya, EEE, O'nyong-nyong, **Ross River**, Sinbis, VEE, WEE
  - Genus Rubivirus (1 species)
    - Rubella





Ross River Virus

- Mosquito-transmitted *Alphavirus (Aedes* spp.*)*
- Endemic /enzootic in Australia and Papua New Guinea
- Most common arboviral disease in Australia
  - Thousands of cases annually (avg. 4,745; 1991-2000)
- Classic syndrome
  - Constitutional symptoms, rash, rheumatic man

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2001, p. 909–932
0893-8512/01/$04.00+0 DOI: 10.1128/CMR.14.4.909–932.2001

Ross River Virus Transmission, Infection, and Disease: a Cross-Disciplinary Review

DAVID HARLEY,[1,2] ADRIAN SLEIGH,[1]* AND SCOTT RITCHIE[2]

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2001, p. 909–932

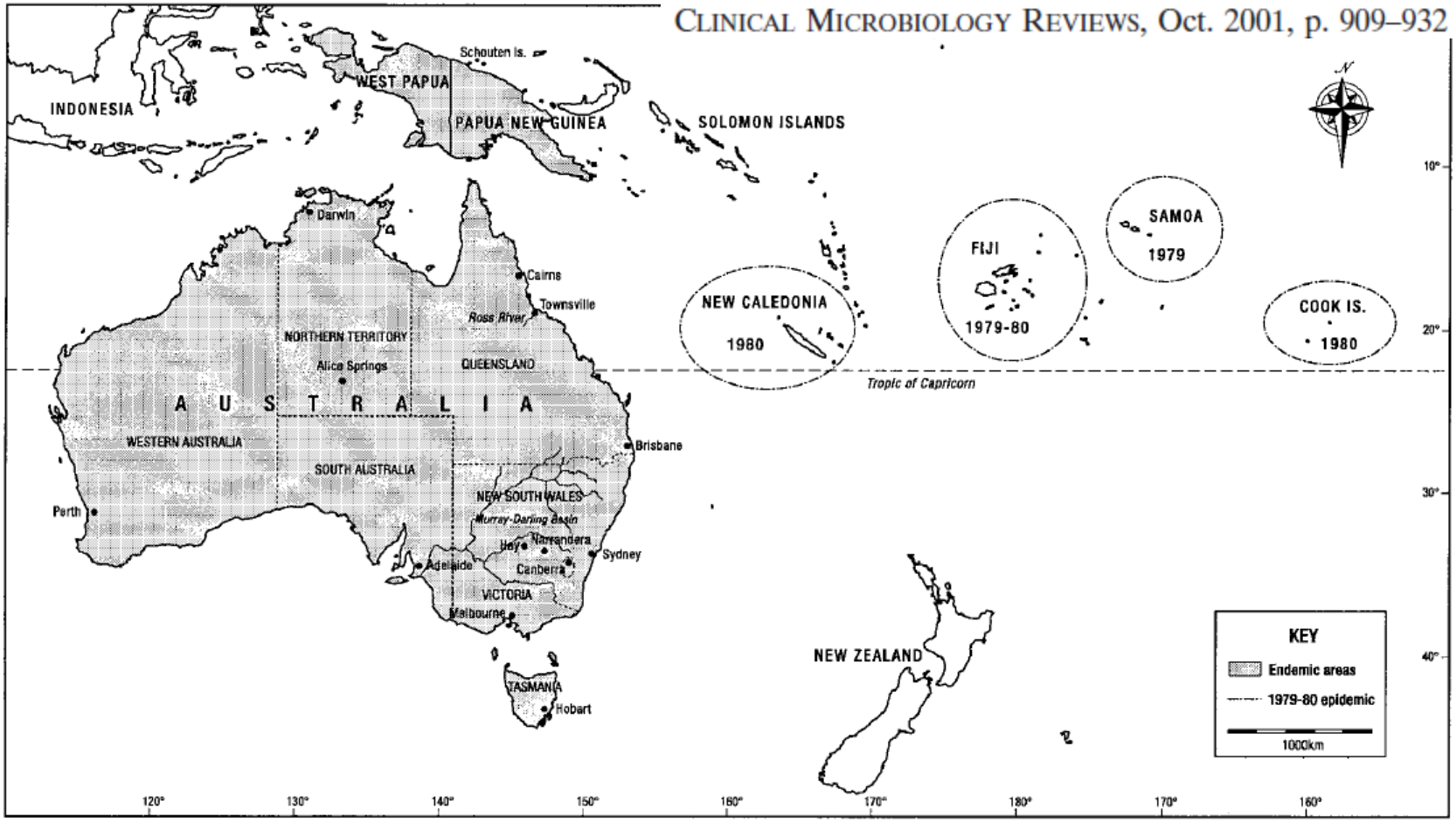
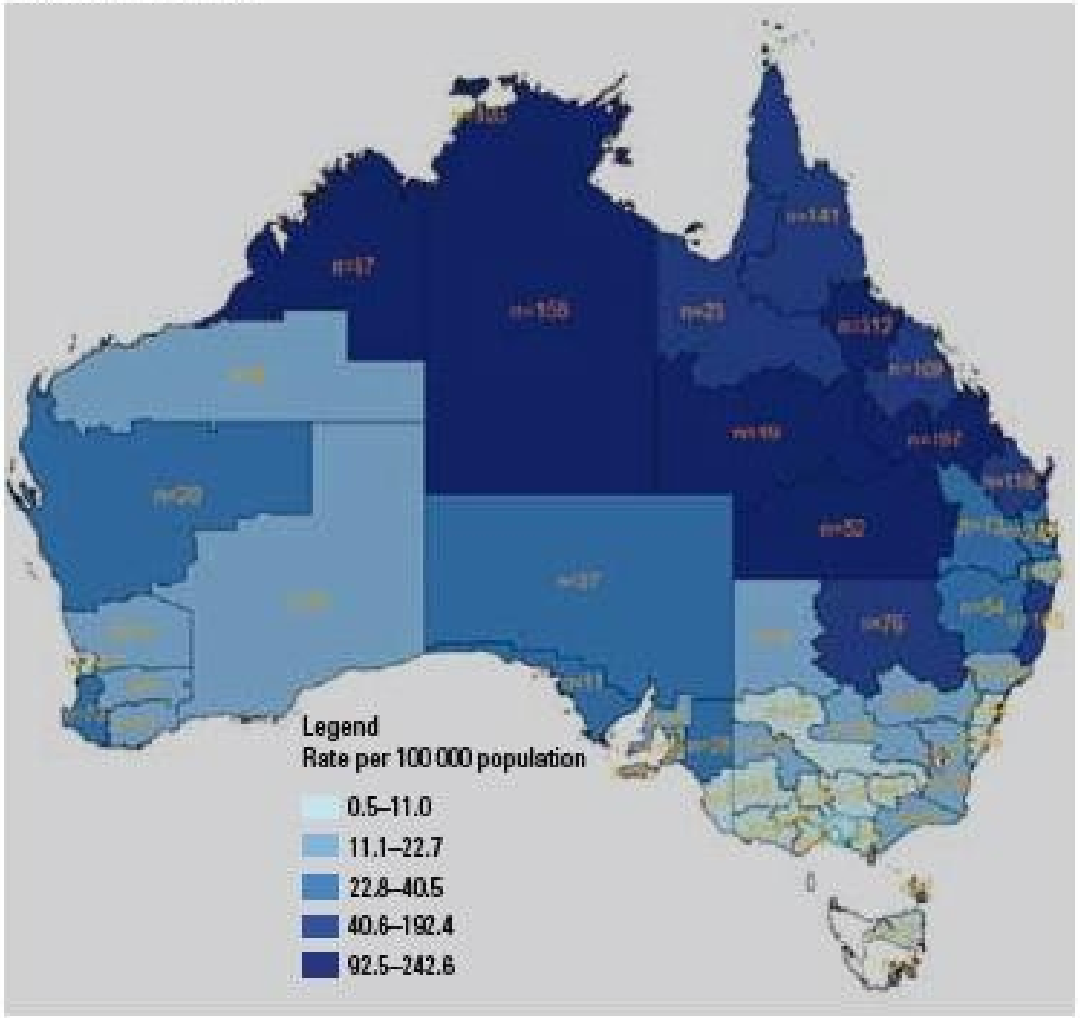


FIG. 1. Map showing cities, towns, and geographical features discussed in the text, areas where RRV is endemic, and the 1979 to 1980 South Pacific epidemic of RRV disease.

Figure 1. Notifications and notification rates of Ross River virus infections, Australia 2006–2007



Reproduced from: Liu C, Begg K, Johansen C, et al. Communicable Diseases Network Australia National Arbovirus and Malaria Committee Annual Report, 2006–2007. Map 2 – Notifications and notification rates of RRV infections, Australia, 2006–07. Comm Dis Intell 2008;32:1. ©Commonwealth of Australia. Reproduced with permission

Ross River Virus Clinical Manifestations

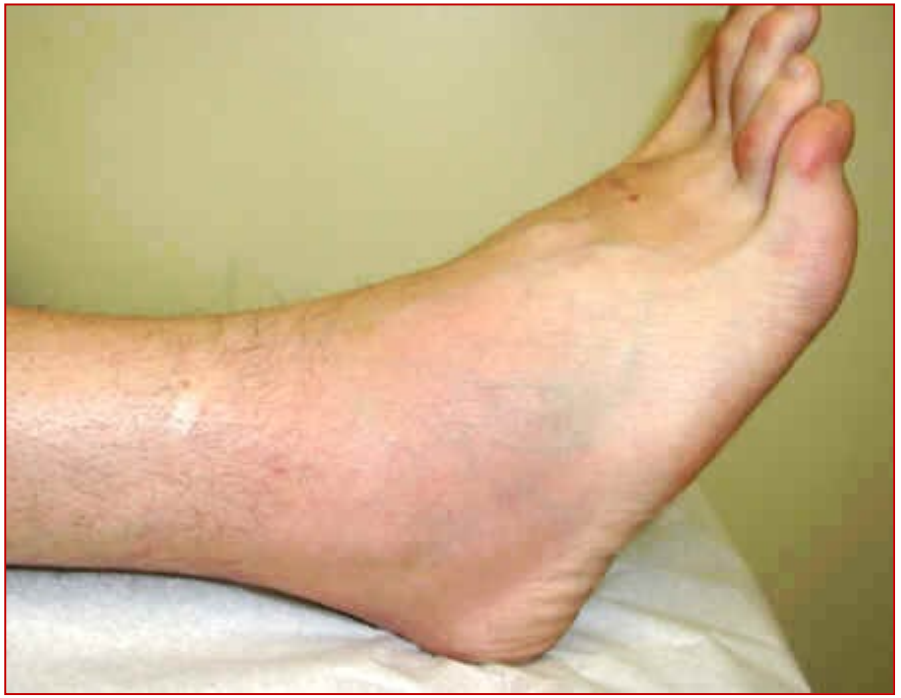
- RRV incubation period ~7 to 9 days
- Asymptomatic infections in ~30%
- Symptoms may last for months or longer (co-morbidities)

- Constitutional symptomatology
  - Fever (1/3 to 1/2 of patients)
  - Rash, fever, and arthralgia may occur in any sequence
  - Fatigue typically affects over 50% of patients
  - Myalgia is common
  - Lymphadenopathy occurs quite often
  - Sore throat and coryza less frequently
  - Diarrhea is rare

- Joint manifestations
  - Symmetrical and acute in onset
  - Tenderness with minor restriction of movement
  - May have extreme redness and swelling
  - Effusions are common
  - Peripheral joints are predominantly involved
  - Ankles, fingers, wrists, and knees commonly affected

http://www.bing.com/images/search?q=Ross+river+virus&Form=R5FD0#view=detail&id=2AC4DDD2BF5E090FC561D2C0F252A08D93D7BE63&selectedIndex=32

Accessed 9 SEP 2013



- Rash
  - Usually lasts 5 to 10 days
  - May be the sole manifestation of infection
  - Appears mainly on the limbs and trunk
  - Maculopapular, vesicular, or purpuric

Reprinted from AUSTRALIAN FAMILY PHYSICIAN Vol. 38, No. 8, August 2009

Table 2. Frequency of symptoms and signs of Ross River virus[20–23]

Symptoms/sign	Frequency (%)
Joint pains	95
Tiredness	90
Fever	50–60
Myalgia	60
Rash	40–60
Headache	50
Joint swelling	50
Depression	45

Ross River Virus Transmission, Infection, and Disease: a Cross-Disciplinary Review

DAVID HARLEY,[1,2] ADRIAN SLEIGH,[1]* AND SCOTT RITCHIE[2]

TABLE 1. Joints affected by RRV disease

Joint	Frequency of joint involvement (% of cases)				
	Seglenieks and Moore (180) (n = 115)	Aaskov et al.[a] (4) (n = 36)	Mudge and Aaskov (144) (n = 400)	Condon and Rouse (33) (n = 189)	Westley-wise et al. (218) (n = 80)
Fingers		50[c]	80	81	63
Hand	45				
Thumb			53	58	
Wrist	36	70	80	100	61
Elbow	17	40	44	71	
Shoulder		38	47	62	
Hip	4	10	27		
Knee	39	80	80	100	64
Ankle	50	78	88	97	64
Feet	49	36			
Toes			47		
Back	14[b]	36	37	56	
Neck		36	12	70	
Jaw			10	15	

[a] Percentages taken from a bar graph.
[b] Includes back or neck.
[c] Includes fingers and hand.

- Diagnosis
  - Serology
    - Acute and convalescent samples (14 days apart)
    - Demonstrate 4 fold rise in IgG antibody
  - Neutralizing antibodies by PRNT
  - Identify peripheral RNAemia (?)

- Treatment
  - No known treatment which alters disease course
  - Treat symptoms
    - NSAIDS
    - Physical therapy, hydrotherapy, etc.
    - Reassurance

Question

- 50 yo Indian male presents with complaints of chronic pain and mild swelling in his fingers, bilaterally. He has no significant medical history except for a febrile illness he experienced 3 months ago following a trip to visit his family in southern India. He recalls the illness including fever, headache, fatigue, rash, and severe joint pain which lasted for ~9 days and spontaneously resolved without specific treatment. All symptoms resolved except for the joint pains which is why he presents today.

- What illness did the man experience following his trip 3 months ago?
  - A. Chikungunya
  - B. Dengue
  - C. Leptospirosis
  - D. Ross River virus
  - E. Enteric fever

Arboviruses

- Family Togaviridae
  - Genus Alphavirus (30 species, examples below)
    - Barmah Forest, **Chikungunya**, EEE, O'nyong-nyong, Ross River, Sinbis, VEE, WEE
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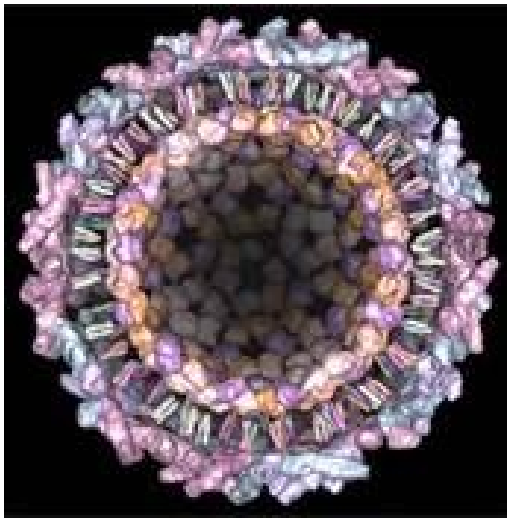
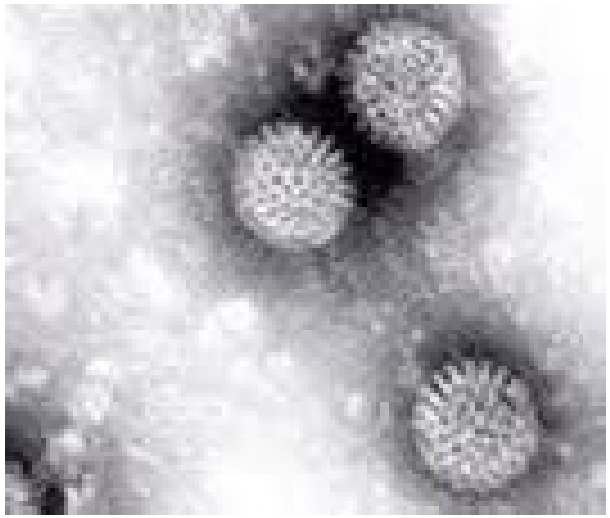
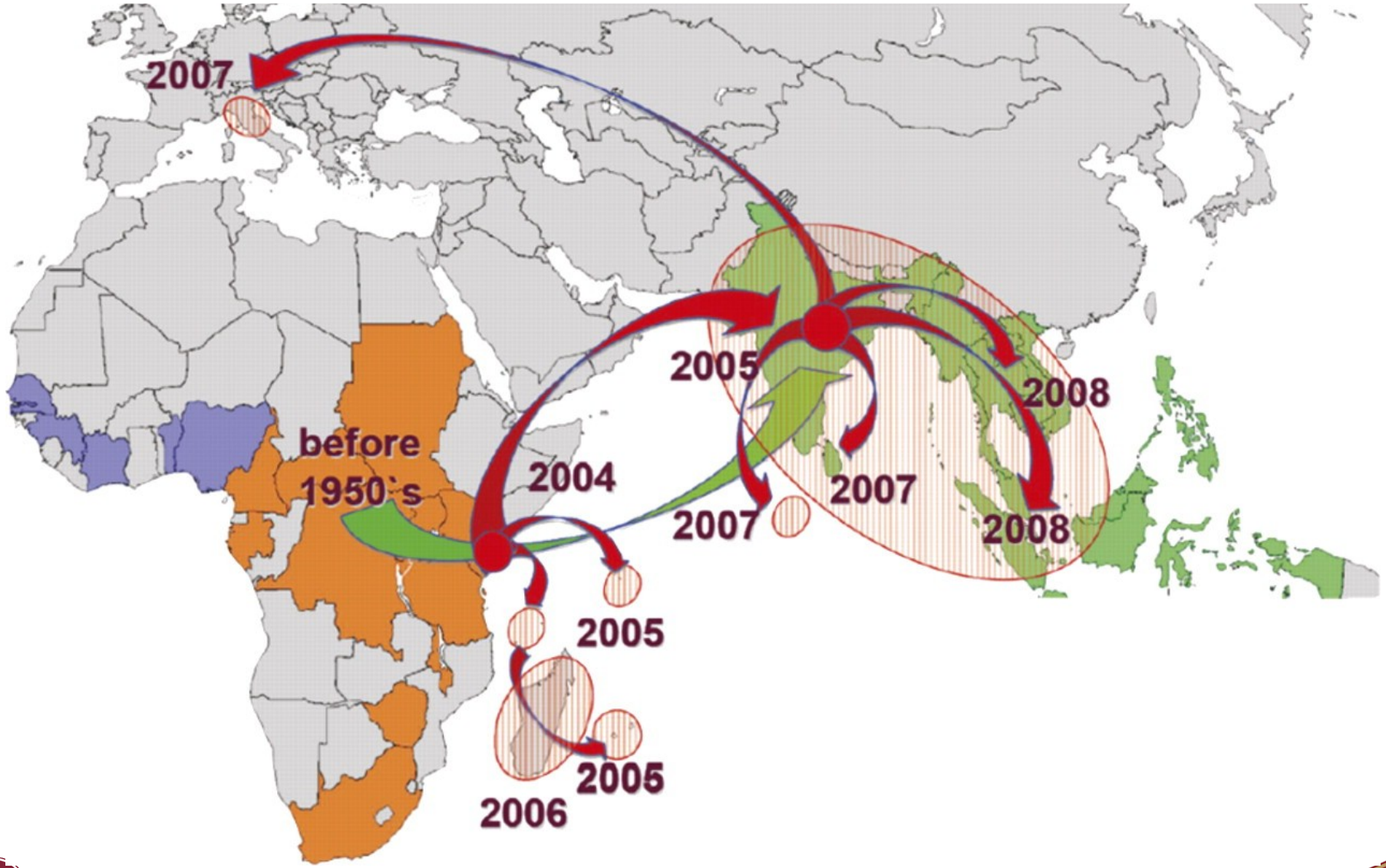




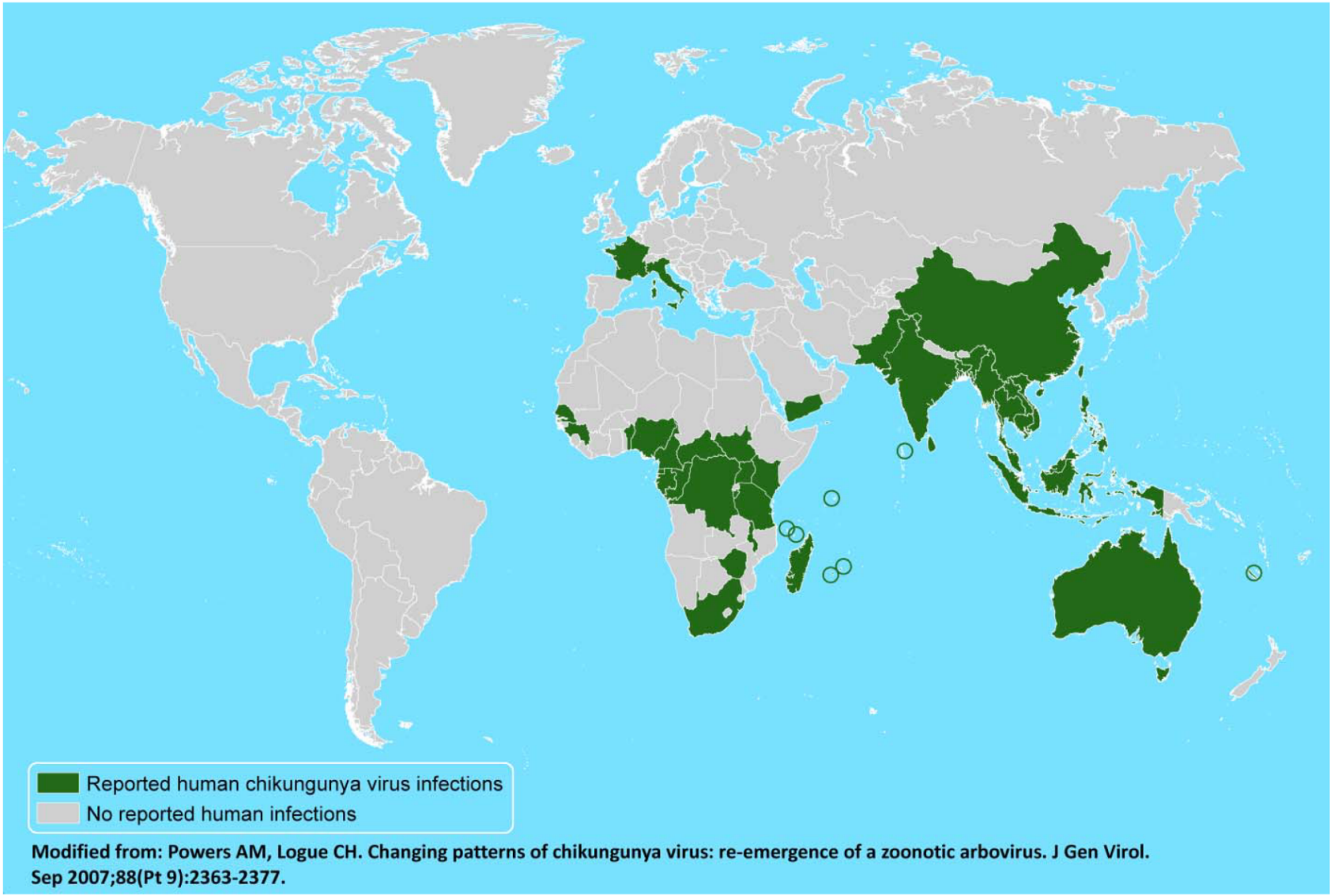
Chikungunya

- Mosquito-transmitted *Alphavirus (Aedes* spp.*)*
- Historically, epidemic transmission patterns
  - Potential of sustained transmission in SE Asia?
- Recent outbreaks have infected hundreds of thousands
  - High clinical attack rates observed
  - Mortality increasingly observe
- Classic syndrome
  - Fever with polyarthritis

Historic Movement of Chikungunya

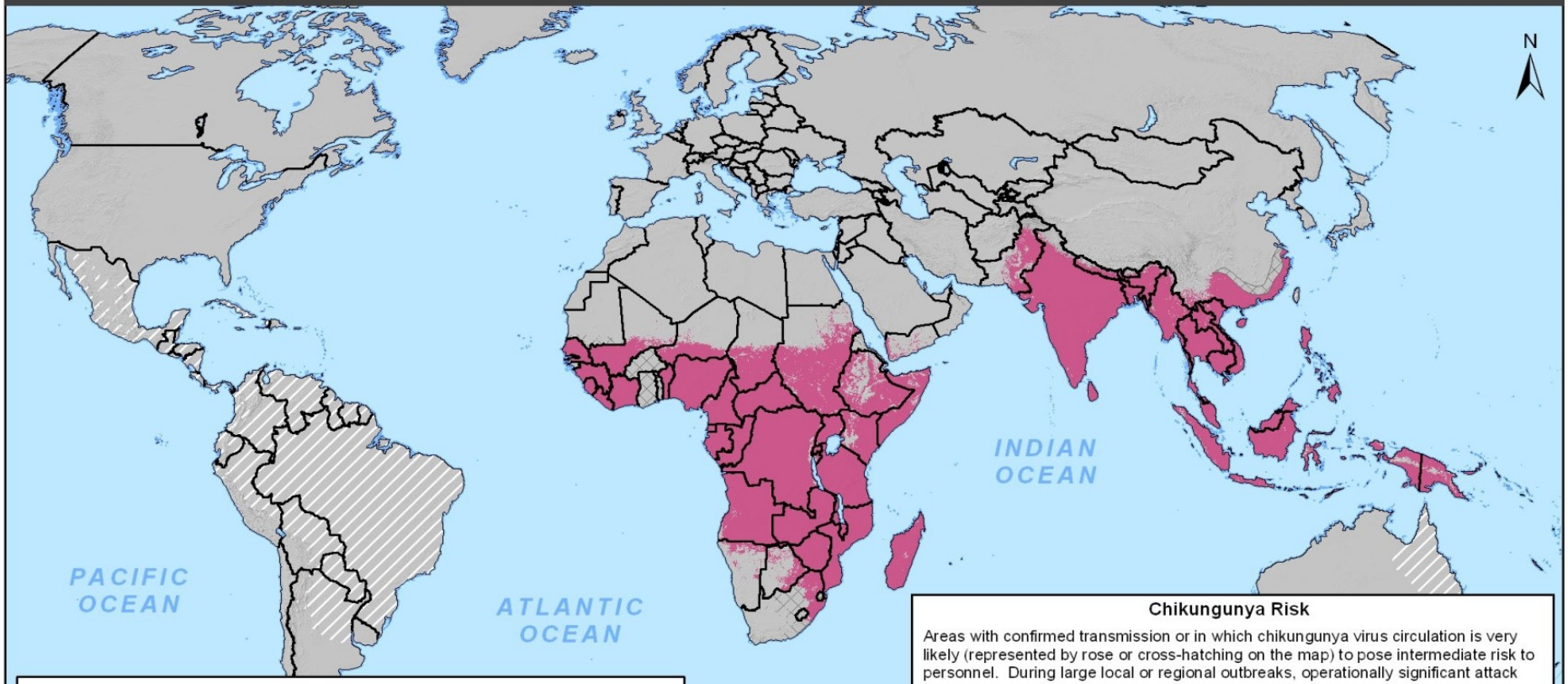


Infections: US CDC as of MAY 2012



Modified from: Powers AM, Logue CH. Changing patterns of chikungunya virus: re-emergence of a zoonotic arbovirus. J Gen Virol. Sep 2007;88(Pt 9):2363-2377.

Worldwide: Chikungunya Risk to U.S. Forces



Note on Transmission and Risk

Because the vectors and epidemiology of dengue fever and chikungunya are very similar, the potential distribution of chikungunya parallels the known distribution of dengue fever. Chikungunya transmission and outbreaks are more intermittent and unpredictable than those seen in dengue. Intensity and duration of outbreaks are expected to be higher as population density increases. Outbreaks occur during the rainy season when day-biting mosquitoes are abundant and virus is introduced by an infectious person into a susceptible and densely populated area. The level of population immunity (known as herd immunity) is a major driver of chikungunya risk. In areas which have had recent outbreaks, herd immunity is high, making the risk of a subsequent outbreak very low for many years. As an increasing number of susceptible individuals are born into the population, the overall herd immunity declines. When population immunity is sufficiently low, explosive outbreaks often occur if/when the virus is introduced.

Chikungunya Risk

Areas with confirmed transmission or in which chikungunya virus circulation is very likely (represented by rose or cross-hatching on the map) to pose intermediate risk to personnel. During large local or regional outbreaks, operationally significant attack rates of 1-50% per month could occur among personnel exposed to mosquito bites.

- Chikungunya has been identified at the country level. Areas are assessed as environmentally suitable for chikungunya transmission.
- Chikungunya has not been reported but vectors are present, areas are environmentally suitable for transmission, the likelihood of introduction is high, and disease surveillance is limited (therefore transmission is likely to occur undetected).
- Currently no risk – in these areas mosquito vectors are present, chikungunya circulation has not been detected despite adequate surveillance and diagnostic capabilities; however, dengue transmission is known occur.
- No risk. Environmental conditions are unsuitable for transmission.

NOTE: This map is based on analyst judgment, using epidemiologic data, remote sensed environmental data, geospatial population density data, and U.S. government risk assessment methodology. Boundaries of risk areas are approximate, and should not be interpreted as strict demarcations.

Clinical Manifestations

- Clinical attack rates vary by population (25-90%)
- Children and older adults with co-morbidities experience largest burden of disease
- High rates of hospitalization (66% in one study) reported
- Emerging reports of significant case fatalities
- Chronic phase of disease becoming increasingly reported

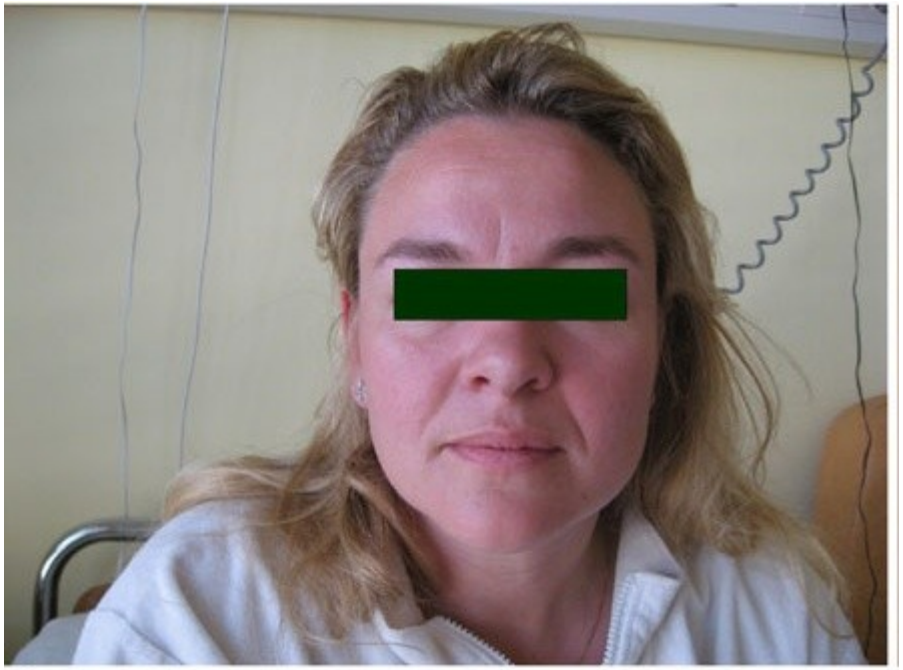
Clinical Manifestations

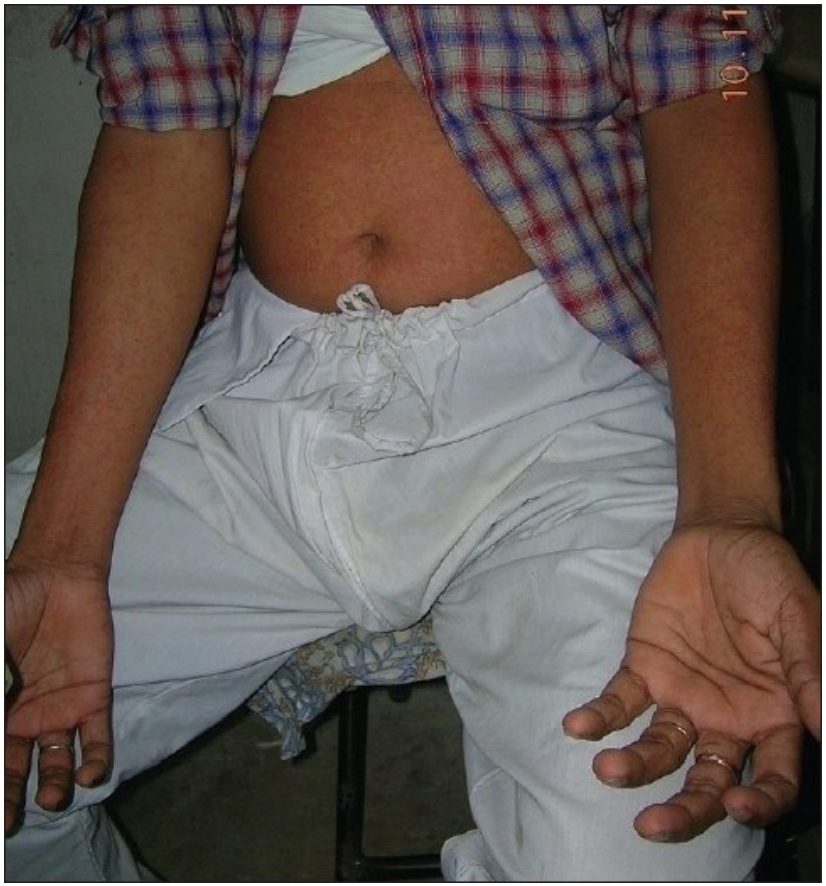
Symptom or sign	Frequency range (% of symptomatic patients)
Fever	76–100
Polyarthralgias	71–100
Headache	17–74
Myalgias	46–72
Back pain	34–50
Nausea	50–69
Vomiting	4–59
Rash	28–77
Polyarthritis	12–32
Conjunctivitis	3–56

[a]Table compiled from a number of different studies.[8, 9, 12-17]

Pan American Health Organization
Preparedness and Response for Chikungunya Virus: Introduction in the Americas
Washington, D.C.: PAHO, © 2011

Clinical Manifestations - Rash





Chikungunya vs. Dengue

Clinical and laboratory features	Chikungunya virus infection	Dengue virus infection
Fever (>102°F or 39°C)	+++	++
Myalgias	+	++
Arthalgias	+++	+/-
Headache	++	++[b]
Rash	++	+
Bleeding dyscrasias	+/-	++
Shock	-	+
Leukopenia	++	+++
Neutropenia	+	+++
Lymphopenia	+++	++
Elevated hematocrit	-	++
Thrombocytopenia	+	+++

[a] Mean frequency of symptoms from studies where the two diseases were directly compared among patient seeking care; +++ = 70-100% of patients; ++ = 40-69%; + = 10-39%; +/- = <10%; - = 0% [32, 33]

[b] Often retroorbital

Table modified from Staples et al.[34]

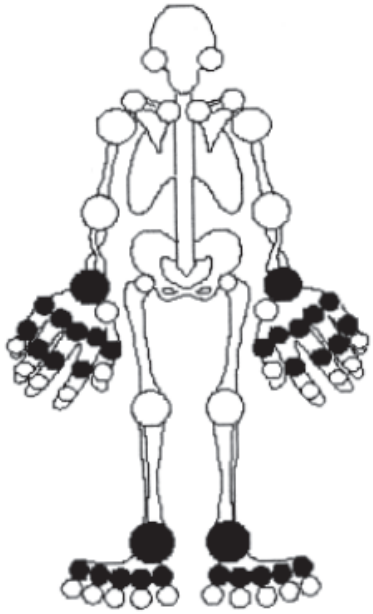


Figure 1. Affected joints (in black) in a patient with CHIKV polyarthritis presenting 6 weeks after onset of illness.

Chikungunya viral polyarthritis.

Raj J Carmona, Saeed Shaikh and Nader A Khalidi

J Rheumatol 2008;35;935-936

Chikungunya: A Potentially Emerging Epidemic?

Michelle M. Thiboutot[1,2], Senthil Kannan[2], Omkar U. Kawalekar[2], Devon J. Shedlock[2], Amir S. Khan[3], Gopalsamy Sarangan[4], Padma Srikanth[4], David B. Weiner[2], Karuppiah Muthumani[2]*

Table 1. Comparison of clinical features of Chikungunya and Dengue virus.

Clinical Features	Chikungunya Virus (CHIKV)	Dengue Virus (DENV)	Reference
1) Fever, asthenia	Common	Common	[6,8]
2) Myalgia	Possible	Very common	[6]
3) Polyarthritis	Very Common, edematous	None	[56]
4) Tenosynovitis	Yes	None	[57]
5) Leukopenia	None	Yes	[58]
6) Thrombocytopaenia	None	Yes	[59]
7) Rash	Days 1–4, important skin edema	Days 3–7	[6,35,58]
8) Retro-orbital pain	Rare	Common	[60]
9) Hypotension	Possible	Common, Days 5–7	[60,61]
10) Minor bleeding	Chronic polyarthritis up to 1 year	Common	[17,56]
11) Second stage	Possible; Tenosynvovitis at M2–M3 Raynaud's syndrome at M2–M3	Fatigue up to 3 mo	[6,56,57,58,62,63]

doi:10.1371/journal.pntd.0000623.t001

Atypical Clinical Manifestations

System	Clinical manifestations
Neurological	Meningoencephalitis, encephalopathy, seizures, Guillain-Barré syndrome, cerebellar syndrome, paresis, palsies, neuropathy
Ocular	Optic neuritis, iridocyclitis, episcleritis, retinitis, uveitis
Cardiovascular	Myocarditis, pericarditis, heart failure, arrhythmias, hemodynamic instability
Dermatological	Photosensitive hyperpigmentation, intertriginous aphthous-like ulcers, vesiculobullous dermatosis
Renal	Nephritis, acute renal failure
Other	Bleeding dyscrasias, pneumonia, respiratory failure, hepatitis, pancreatitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hypoadrenalism

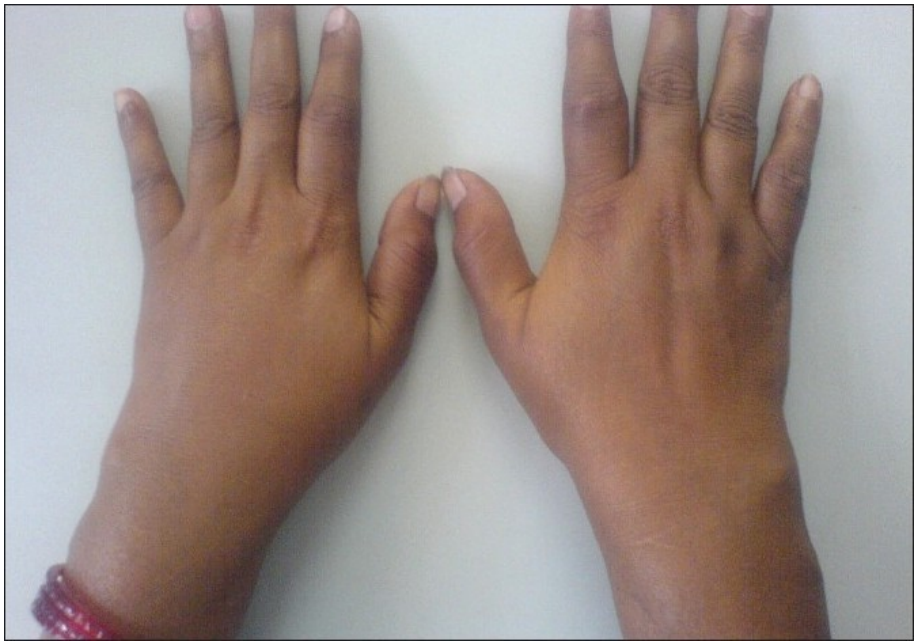
Adapted from Rajapakse et al. [20]

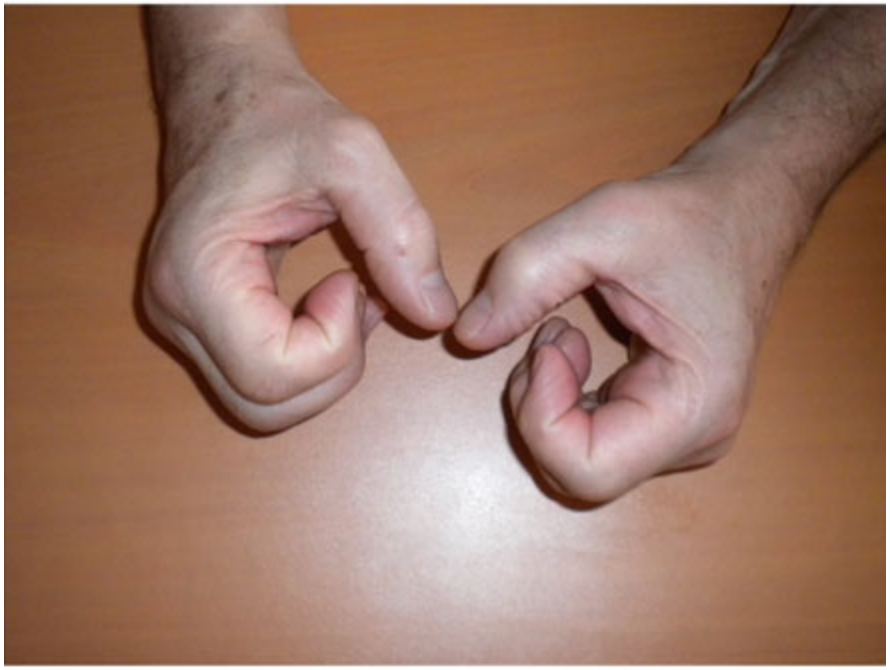
Chronic Chikungunya

Three clinical components, singly /in combination:

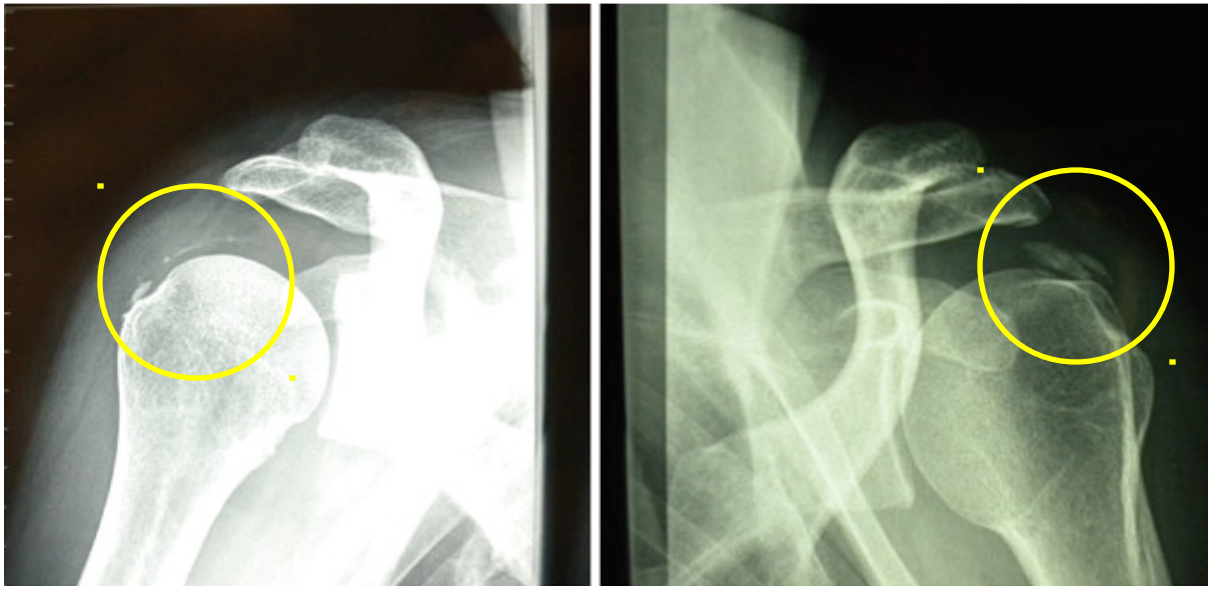
1. Distal polyarthritis / monoarthritis improved with NSAIDs.
2. Frequent tenosynovitides in the hands, wrists, or ankles, sometimes responsible for carpal or tarsal tunnel syndromes, highly sensitive to short-term systemic corticotherapy, and
3. Exacerbation of pain in previously injured joints and bones requiring painkillers.

Chronic Chikungunya

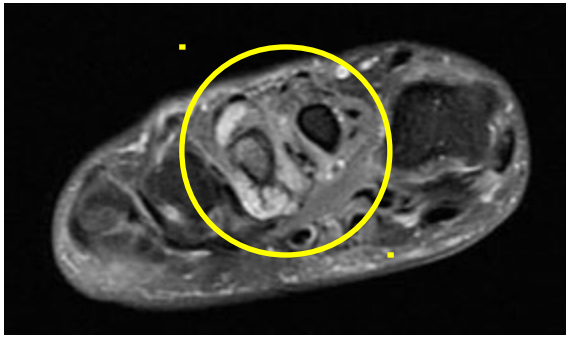


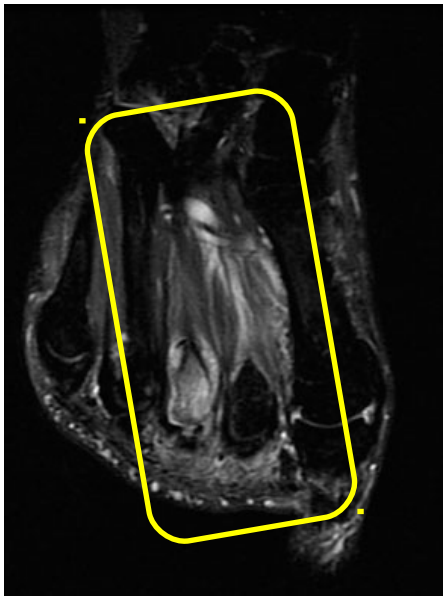


Chronic Chikungunya



Calcifications in shoulder tendon 18 months after infection





Inflammatory osteoarthritis, foot, 5 years after infection

- Diagnosis
  - Viral isolation (very narrow window)
  - Quantitative RT-PCR (peripheral RNAemia)
  - Serology (ELISA, HAI, IFA)
  - PRNT (neutralizing antibodies)

- Treatment
  - No vaccine or antiviral licensed
  - Illness is usually self-limiting
  - Symptomatic treatment only
    - Rest to the patient and mild movements of joints
    - Cold compresses to inflamed joints
    - Liberal fluid intake or IV fluids
    - Analgesics and NSAIDS
  - Convalescence can last weeks to years

Question

- A 67 yo male from presents with a five-day history of a febrile illness, headache, severe abdominal pain, anxiety, nausea and vomiting, dyspnea, jaundice, leukopenia, and thrombocytopenia. He lives in the eastern rain forest of Ecuador. He does not drink ETOH or use tobacco. He is up to date on all immunizations including yellow fever vaccine received 5 days prior to onset of symptoms. On admission, his BP was 110/70, HR of 72, a RR of 20, a temp. of 36°C, and O2 saturation rate of 74% on room air. Three hours after admission, he was transferred to an intensive care unit because of multiorgan system failure, oliguric renal failure. He experienced a cardiac arrhythmia and died.

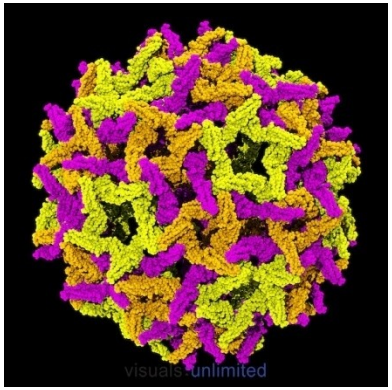
- What is the most likely cause of the patient's demise?

1. Severe dengue
2. YF vaccine-associated neurologic disease (YEL-AND).
3. YF vaccine-associated viscerotropic disease (YEL-AVD)
4. Sylvatic YF

Case Report: Richard W. Douce *Am. J. Trop. Med. Hyg.,* 82(4), 2010, pp. 740–742

Arboviruses

- Family Flaviviridae
  - Genus Flavivirus (53 species, examples below)
    - Dengue, Japanese encephalitis, Kyasanur Forest disease, MVE, Omsk hemorrhagic fever virus, Powassan, Rio Bravo, SLE, TBE, WNV, **Yellow fever**, Zika virus
  - Genus Hepacivirus (1 species)
    - Hepatitis C virus
  - Genus Pegivirus (2 species)
    - Pegivurs A, Pegivurs B
  - Genus Pestivirus (4 species)
    - Border disease virus, Bovine viral diarrheal virus 1, Bovine diarrheal virus 2, Classical swine fever virus

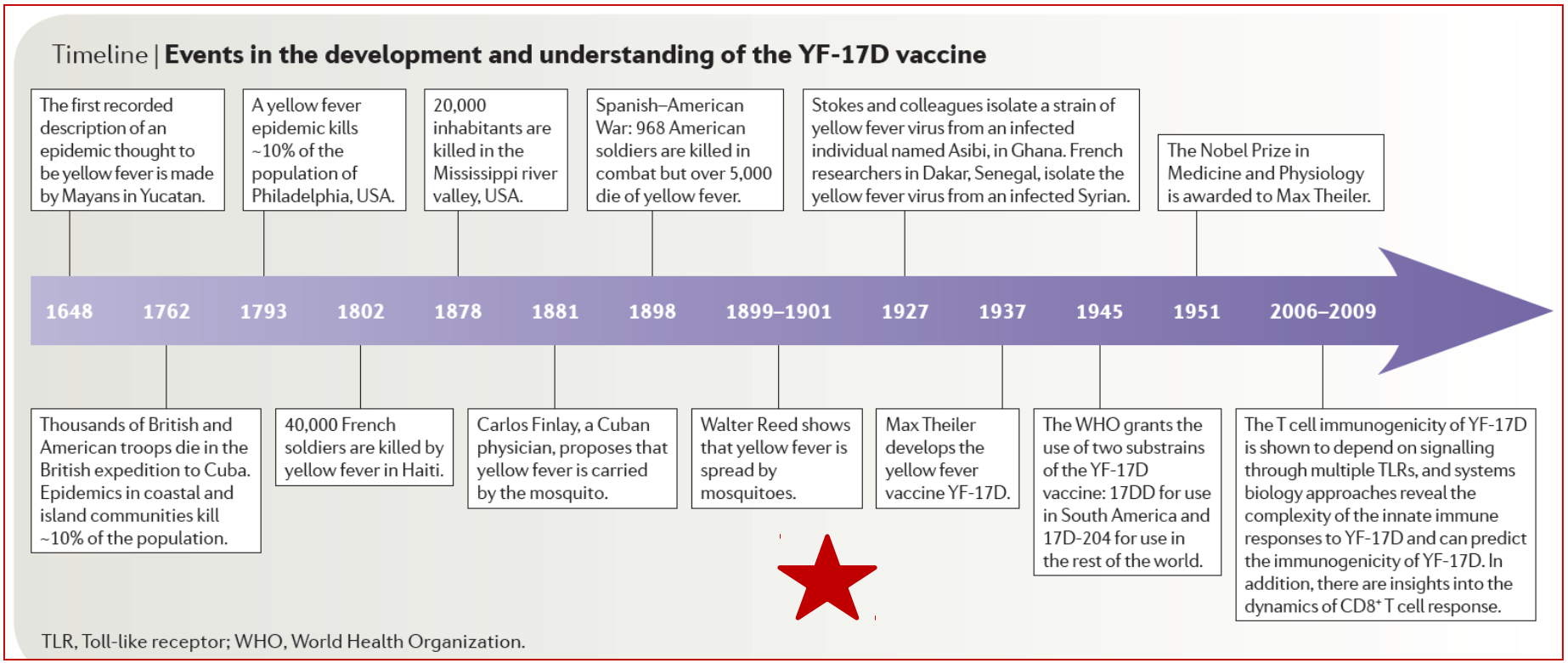


Yellow Fever

Learning immunology from the yellow fever vaccine: innate immunity to systems vaccinology

Bali Pulendran

NATURE REVIEWS | IMMUNOLOGY VOLUME 9 | OCTOBER 2009 | 741



Walter Reed Yellow Fever Commission

- Experiment summary
  - 14 non-fatal human challenge cases of YF produced
  - Transmission cycle revealed
  - Reed et al. publish results in JAMA, 1901
  - Army orders Gorgas to complete source reduction

Havana in 1900

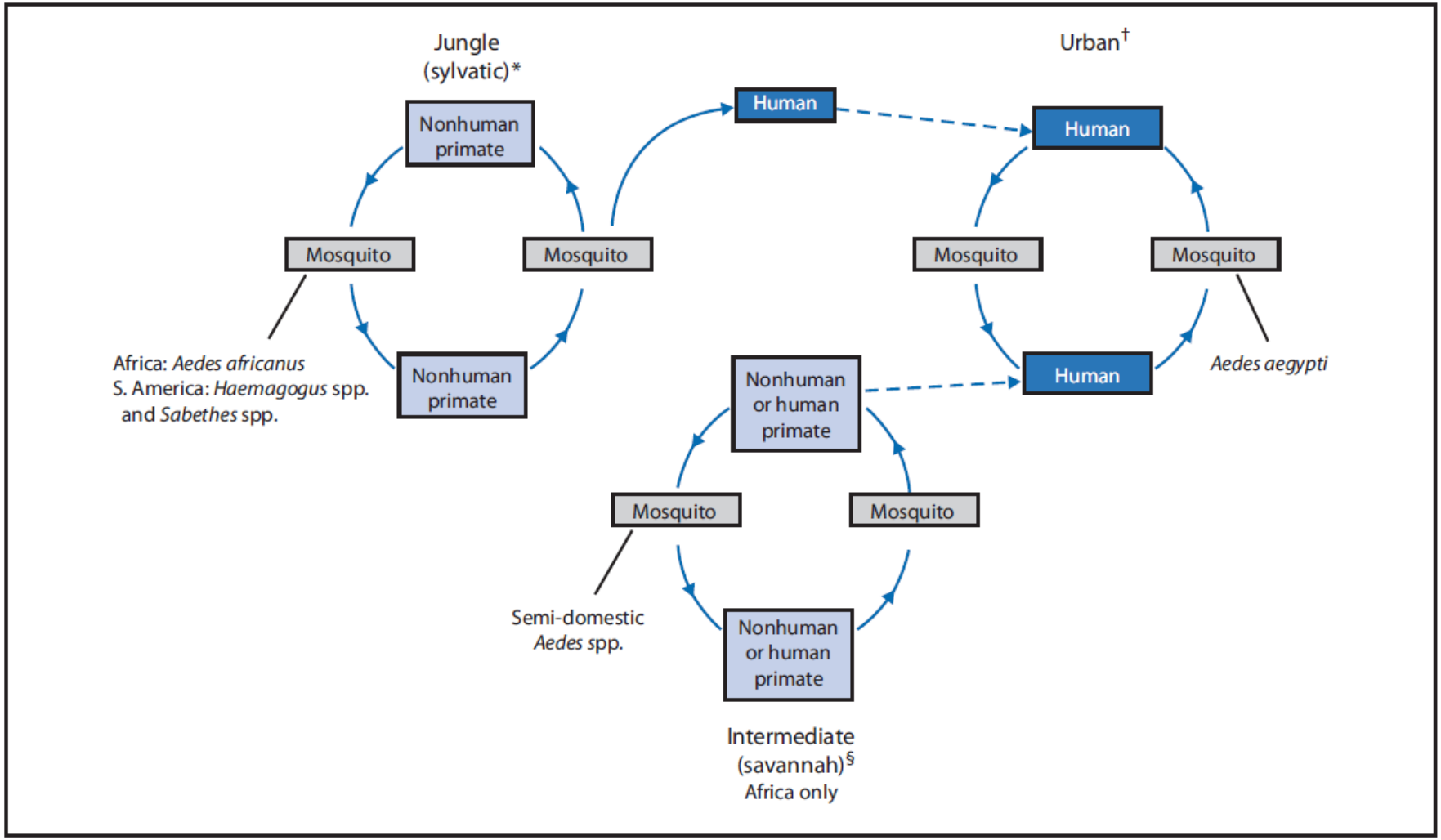
Yellow Fever Virus

- Virus
  - Flavivirus (YF, JE, WNV, DENV)
  - 1 serotype
    - 5 genotypes within serotype

- Vector
  - Mosquito (*Aedes* spp.)

- Phylogenetic analyses
  - Evolved over 3000 yrs
  - YF virus originated in Africa
  - Divided into West and East African lineages
  - W. African lineage
    - Imported into S. America and New World

FIGURE 1. Transmission cycles for yellow fever virus



* The jungle (sylatic) transmission cycle involves transmission of the virus between nonhuman primates and mosquito species found in the forest canopy. The virus is transmitted via mosquitoes from nonhuman primates to human when the humans encroach into the jungle during occupational or recreational activities.

† The urban transmission cycle involves transmission of the virus between human and urban mosquitoes, primarily *Ae. aegypti*. Viremic humans traveling from one region to another can feed into and serve as a source of infection for mosquitoes in other transmission cycles (dotted line).

§ In Africa, an intermediate (savannah) cycle involves transmission of YFV from tree hole-breeding *Aedes* spp. to humans living or working in jungle border areas. In this cycle, the virus can be transmitted from nonhuman primate to humans or from human to human via these mosquitoes.

Yellow Fever Risk Map

Figure 3: Areas with risk of yellow fever virus transmission in South America, 2010

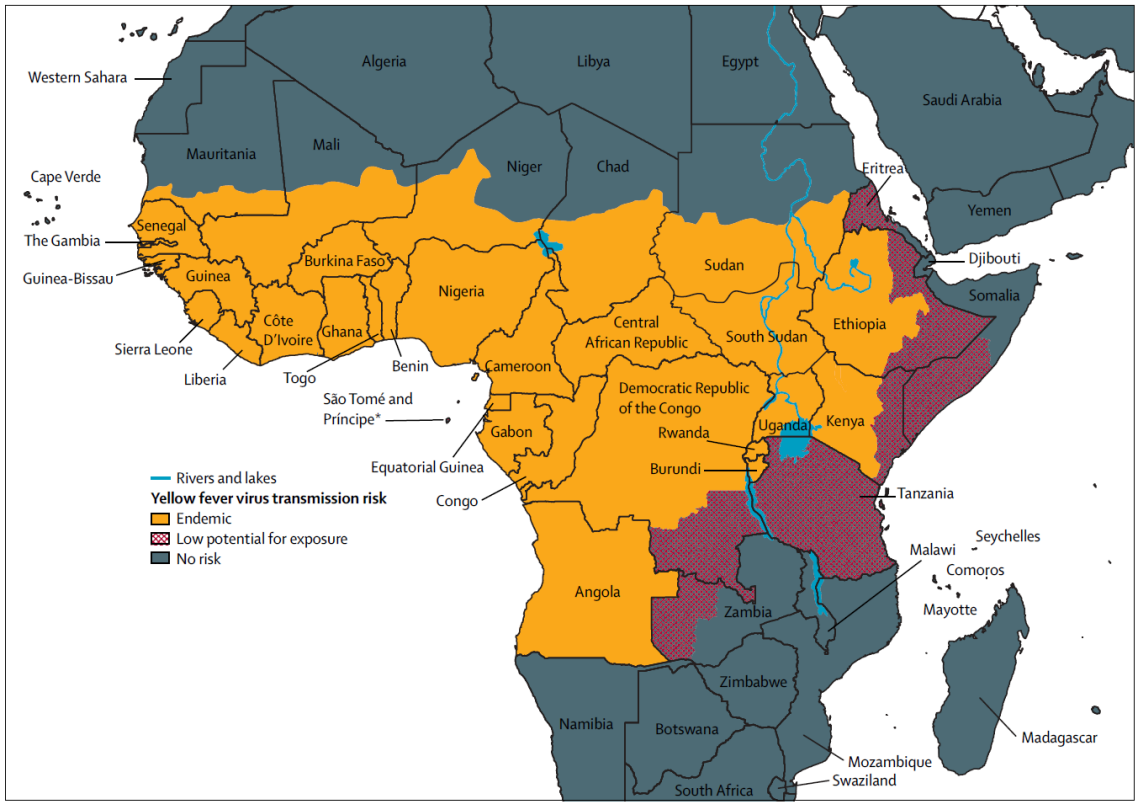


Figure 4: Areas with risk of yellow fever virus transmission in Africa, 2010
*São Tomé and Príncipe was classified as low potential for exposure.

Map is from the following publication: Jentes ES. Poumerol G, Gershman MD, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. Lancet Infect Dis. 2011;11:622-32.

Disease Time-course

- Incubation period: 3-6 days
- Symptoms for ~ 3 days (viremia)
- Defervescence and short term improvement (remission)
- Fever and symptoms return (intoxication)
- Improvement (convalescence)

Figure 5. Yellow fever patient during the period of infection. The patient is febrile and acutely ill, with prominent conjunctival congestion. During this pre-icteric phase, the illness is difficult to differentiate from many other infectious diseases. Virus is present in the blood and the patient is infectious for blood-feeding mosquitoes.

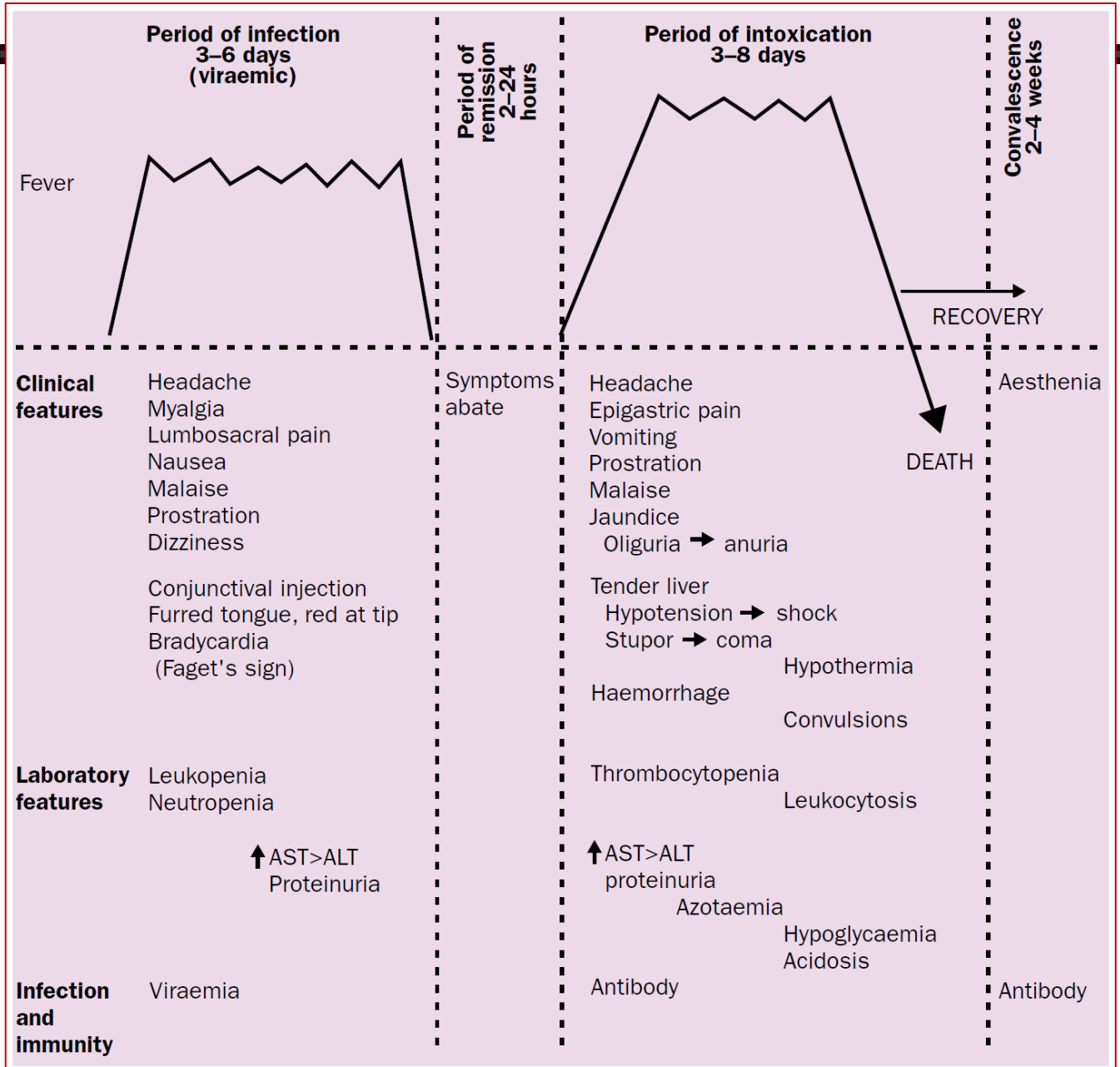


Figure 4. Stages of yellow fever infection, showing the major clinical and laboratory features of the disease.

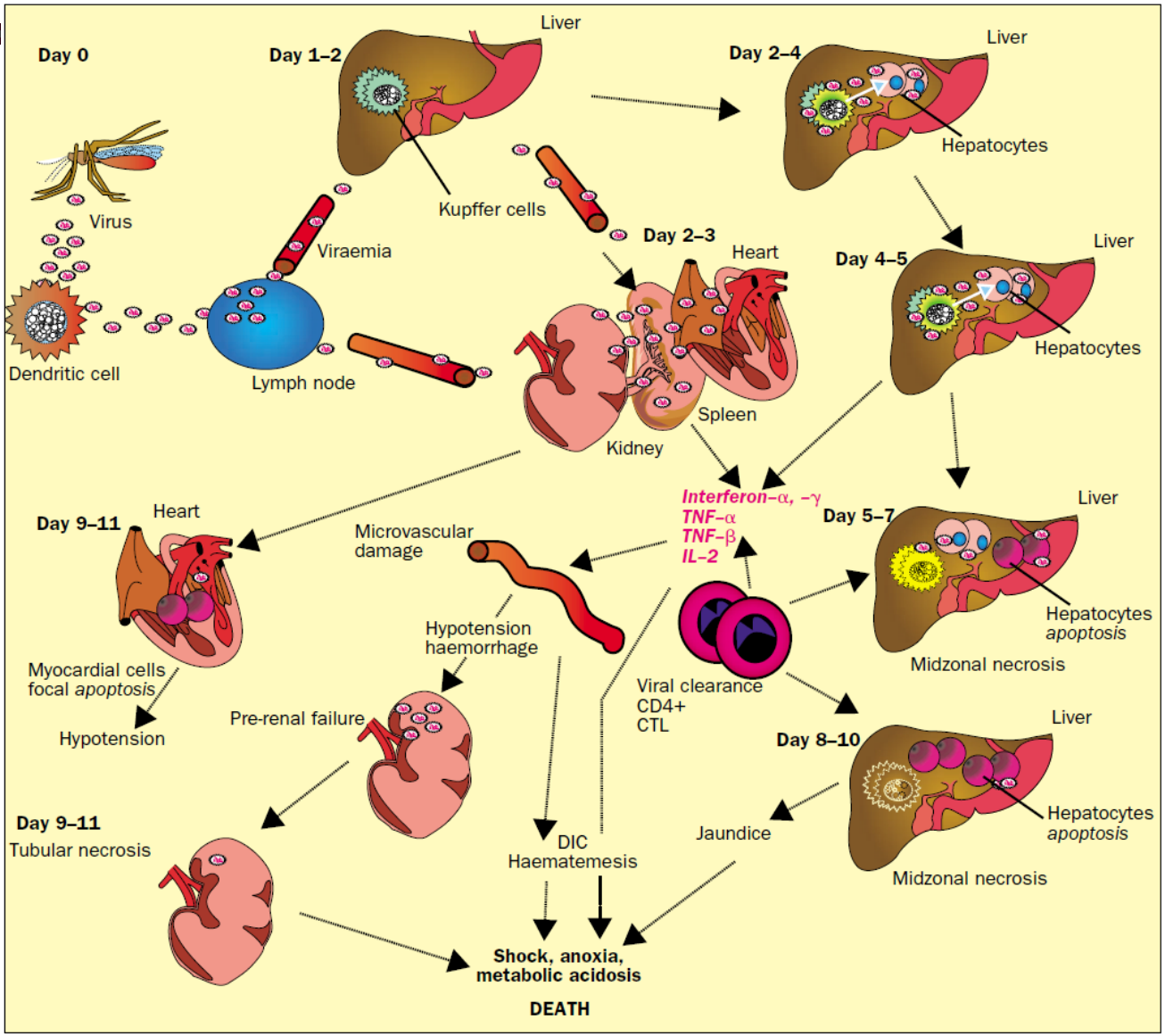


Figure 6. Pathogenesis of yellow fever based on studies in experimentally infected monkeys and human case reports (bold). Speculative mechanisms shown in italics are drawn from in-vitro data or reports on other flavivirus infections. CTL=cytotoxic T lymphocyte, DIC=disseminated intravascular coagulation, IL=interleukin.

Diagnosis

- Clinical Diagnosis
  - h/o travel to endemic area within the incubation period

- Advanced Diagnostics:
  - Virus Isolation (culture)
  - Rapid Diagnostics
    - PCR
      - Remember the window period
    - Antibody or Antigen detection (ELISA)
      - IgM for acute phase, coupled with convalescent antibodies (IgM/IgG)
    - Neutralization Ab are more specific for YF

Treatment Overview

- Supportive Care -- no specific therapy
  - Maintain nutrition and prevent hypoglycemia
  - NG tube to prevent gastric distention
  - Treatment of hypotension (IVF, pressors)
  - Supplemental oxygen
  - Correction of bleeding abnormalitie
  - Dialysis
  - Treatment of secondary infections
  - Treatment of DIC
  - PROTECT FROM FURTHER MOSQUITO EXPOSURE

Certain medications should be avoided, such as aspirin or other non-steroidal anti-inflammatory drugs (such as ibuprofen and naproxen), because these may increase the risk for bleeding.

Yellow Fever Vaccine 17D

- Has remained in continuous use since 1936
  - Over 400 million doses given
  - Protects 90%/10 days, 99%/30 days

- Long-lasting immunity
  - Countries may require boosting every 10 years
  - Studies have shown neutralizing Ab decades after dose
    - 81% of US WWII veterans with Ab after > 30yrs

1. WHO. The Immunological Basis for Immunization Series. Module 8: Yellow Fever.
2. Poland JD, Calisher CH, Monath TP. Persistence of neutralizing antibody 30-35 years after immunization with 17D yellow fever vaccine. Bull World Health Organ 1981;59:895-900.

Table 1. Yellow fever vaccine contraindications and precautions.

Contraindications
Age, <6 months
Thymus disease or history of thymus disease
Immunosuppression
Precautions
Age, 6–12 months
Age, ⩾60 years for first-time vaccinees
Pregnancy
Lactation
Asymptomatic HIV infection with laboratory verification of adequate immune system function
Hypersensitivity to eggs
Hypersensitivity to gelatin
Family history of adverse events associated with yellow fever vaccine

Yellow Fever Vaccine Reactions

- Common
  - Fever, Headache, body aches 5-10 days
  - Injection site inflammation 1-5 days

- Severe
  - Hypersensitivity reactions (including anaphylaxis)
  - YF vaccine-associated neurologic disease (YEL-AND)
  - YF vaccine-associated viscerotropic disease (YEL-AVD)

Yellow Fever Vaccine Reactions

Viscerotropic (hepatotropic) infection:

- transient viremia
- damage to liver, spleen, kidneys and heart
- hemorrhage
- in nature, occurs only in humans and non-human primates
- molecular mechanisms of infection type are poorly understood

Neurotropic infection:

- infects brain parenchyma and causes encephalitis
- in nature, occurs in susceptible rodents
- in "nature" wild-type viruses do not result in neurotropic disease
- can occur in primates when vaccine strain "reverts" to virulent phenotype→ Vaccine Associated Neurotropic Disease

Current Opinion in Immunology

Yellow Fever Vaccine Reactions

YEL-AND

- primary vaccinees
- 2 to 30 days post-vaccination
- fever (>101.5 °F > 24h) and headache (>24h duration)
- focal neurological dysfunction (aphasia, paresis, etc)
- mental status change
- new-onset seizure or recurrence
- CSF pleocytosis (> 5 WBC/mm^3) or elevated protein (>1.5 times normal)
- three distinct clinical entities
  - neurotropic disease
  - auto-immune CNS disease
  - auto-immune PNS disease
- recovery in 95% (CFR <5%)

YEL-AVD

- primary vaccinees
- 2 to 5 days post yellow fever vaccination
- fever, myalgia and arthralgia
- elevated liver enzymes and bilirubin, sometimes progressing to liver failure
- thrombocytopenia, lymphocytopenia
- rhabdomyolysis
- hypotension, requiring vasopressors
- renal failure, requiring dialysis
- respiratory failure, requiring intubation
- recovery in 40% (CFR > 60%), with higher CRF in women

Current Opinion in Immunology

Question

- A 43 yo male is traveling on business throughout Southeast Asia. He will be traveling for 3 weeks (August) staying in hotels located in major urban centers. Tourist activities are planned in rural areas in Northern Thailand, Viet Nam and Cambodia. Activities will include elephant treks, river rafting, and camping. A previous trip to the same region was abruptly cancelled 4 years ago. He recalls receiving 1 dose of a vaccine to prevent a “brain infection.” He has no medical history. He has received all routine childhood vaccinations without adverse events. He has taken doxycycline for malaria prophylaxis in the past without adverse events.

- What is your guidance to the patient regarding Japanese encephalitis?

1. Nothing, he is going to non-endemic areas during a low risk period.
2. JE risk is high where he is travelling and during the period he is travelling, he should ensure use of personal protective measures (PPMs).
3. JE risk is high, he should receive the final 2 doses of the JE vaccine series he started 4 years ago.
4. JE risk is high, he should receive a new, complete series of JE vaccine and use PPMs during his trip.

Arboviruses

- Family Flaviviridae
  - Genus Flavivirus (53 species, examples below)
    - Dengue, **Japanese encephalitis**, Kyasanur Forest disease, MVE, Omsk hemorrhagic fever virus, Powassan, Rio Bravo, SLE, TBE, WNV, Yellow fever, Zika virus
  - Genus Hepacivirus (1 species)
    - Hepatitis C virus
  - Genus Pegivirus (2 species)
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  - Genus Pestivirus (4 species)
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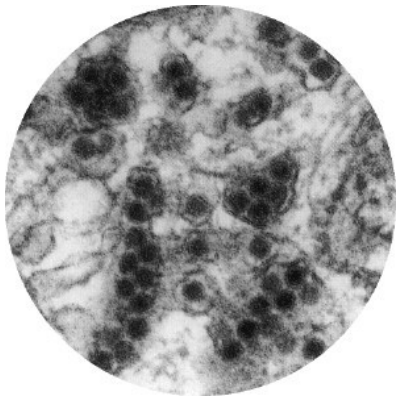


JE Virus

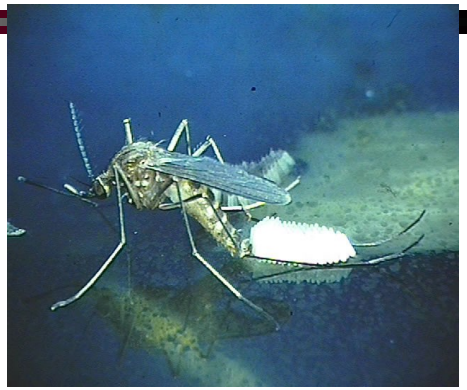
Japanese Encephalitis

- Most common viral encephalitis etiology worldwide
  - 160,000 reported cases 1966
  - 16,000 reported cases 1996
    - Impact of vaccination programs in endemic regions
    - Impact of development, *esp* Japan, Taiwan, ROK
  - Annual estimate is $\geq$ 50K cases
    - 2.5 cases/10,000 population at risk
- Primarily a disease of children
  - Naïve adults at similar risk (i.e., travelers, military)
- Most infections are subclinical/self-limited
  - Clinical cases have high mortality, morbidity
    - CFR ~25 -30%
    - Long-term disability 45 - 50%

Clinical Findings

- Incubation period 4 – 14 days
  - Sudden onset fever, chills and aches
    - Lethargy, HA, meningismus, N/V
  - Acute Flaccid Paralysis
    - Rapid onset paralysis despite normal consciousness
      - Weakness legs > arms, asymmetric
    - Flaccid paralysis also occurs in 5%-20% of comatose patients with "classic" JE
- Course
  - Occasionally fulminant
    - Short prodrome, deep coma, respiratory depression, posturing, death
  - Usually, improvement over ~ 1 week
  - Neuropsychiatric sequelae (years or is permanent)

Transmission

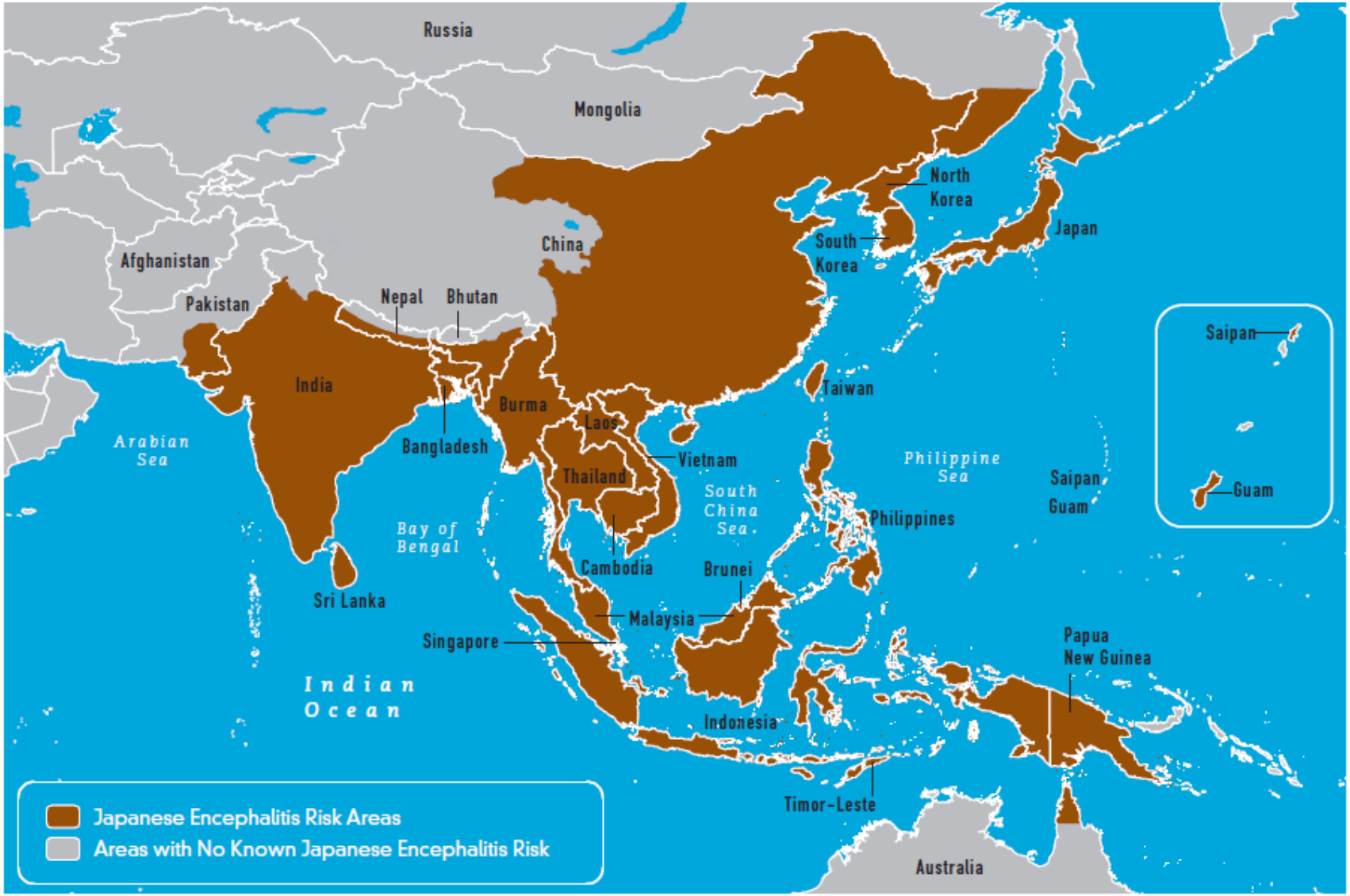


- Vector: *Culex* mosquitoes
  - *Culex tritaeniorhynchus*
    - Breeds in marshes, rice paddies
    - Night-biting

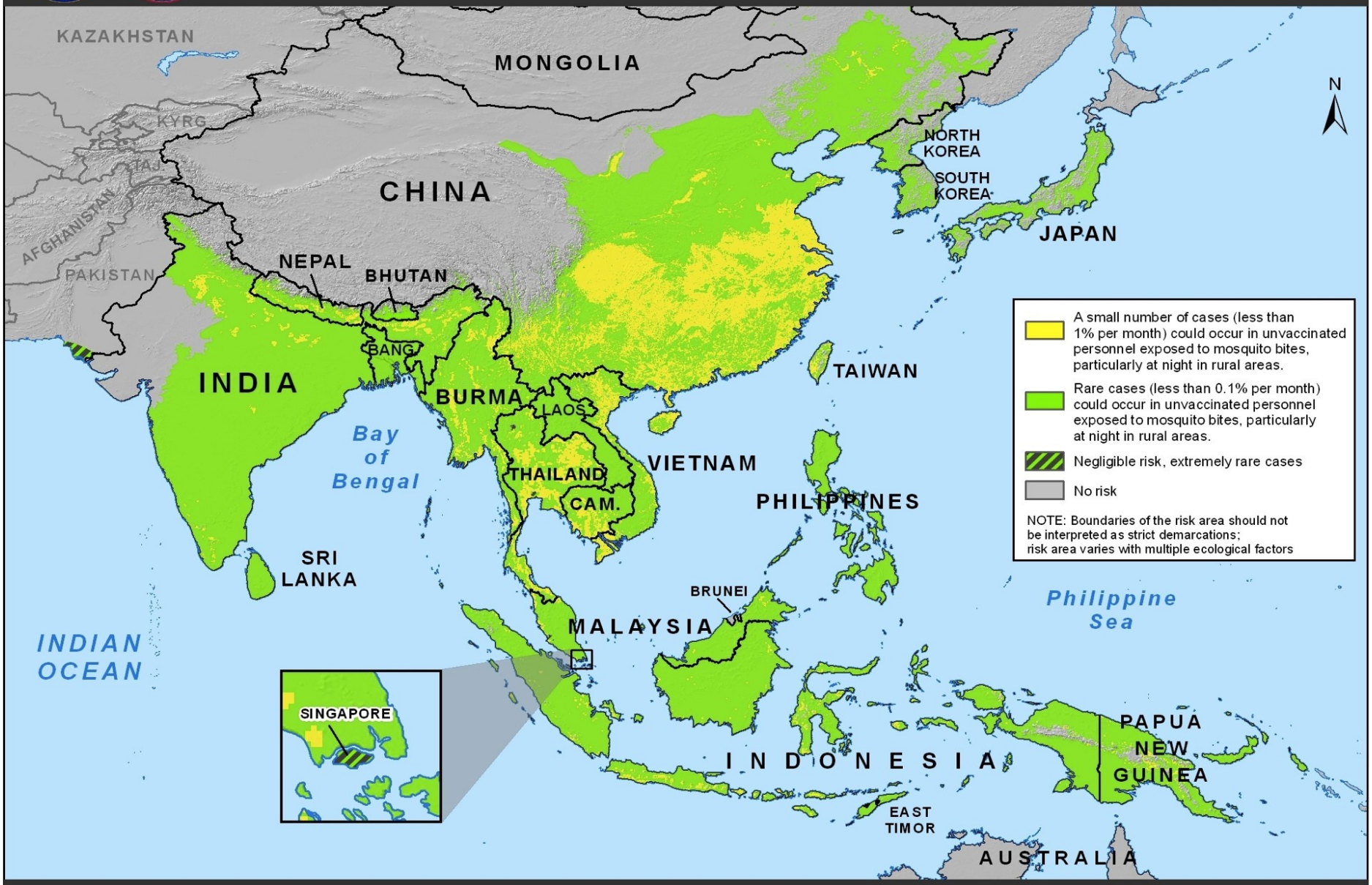
- Zoonotic amplification
  - Domestic pigs
  - Migratory waterfowl

- Seasonal/climate factors
  - Summertime / post-rainy season
    - Increased vector number
    - Increased feeding behaviors
    - Increased viral replication

Japanese Encephalitis



PACOM: Japanese Encephalitis Risk to U.S. Forces



Source: NGA Coordinate System: WGS84

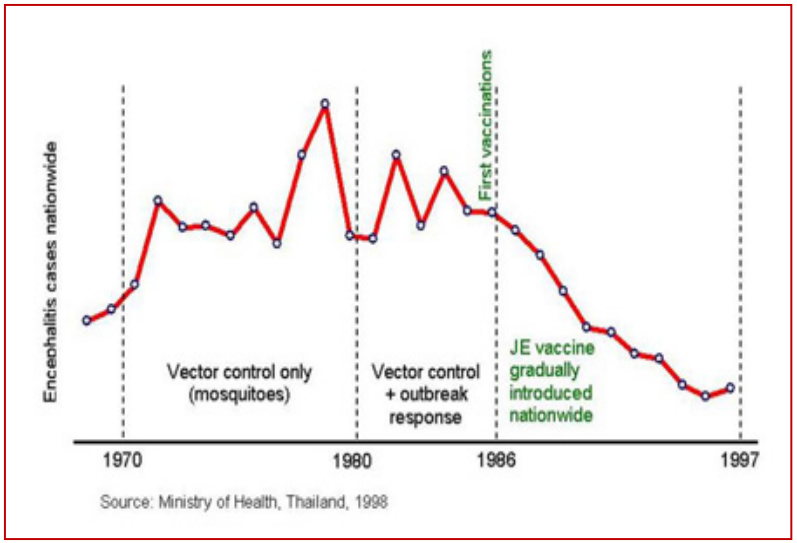
Boundary representation is not necessarily authoritative

Prevention

- Vector control – difficult in endemic regions
  - Impractical, historically ineffective
  - Twilight-biting, marsh-breeding mosquitoes

- Reservoir control – difficult in endemic regions
  - Swine
    - Segregation impractical
    - vaccination expensive

- Vaccination
  - Mass pediatric vaccinations
  - Apparently highly effective



New JE Vaccines

- Live, attenuated SA 14-14-2 vaccine
  - Produced and used successfully in China for > 20 years
- Inactivated vero-cell derived JEV (Biken, Kaketsuken)
  - Inactivated Beijing JEV grown on Vero cells
- ChimeriVax-JE vaccine (Acambis/sanofi pasteur)
  - Live, recombinant vaccine (based on Yellow Fever 17D)
- Ixiaro (Intercell/Novartis/Biological E)
  - Inactivated vaccine
  - Derived from SA-14-14-2 JEV cultured in Vero cells
  - 2 doses at day 0 and day 28
  - Licensed in US for adult use 2009
  - US licensure for pediatric use, May 2013

IXIARO®
Manufacturer's FDA-approved labeling

- INDICATIONS AND USAGE
  - Indicated for active immunization for the prevention of disease caused by JEV in persons 17 years of age and older.
- DOSAGE AND ADMINISTRATION
  - 2 doses administered 28 days apart.
  - Each 0.5mL dose is administered intramuscularly
  - Series should be completed at least 1 week prior to exposure
- CONTRAINDICATIONS
  - Severe allergic reaction(e.g., anaphylaxis) after a previous dose of IXIARO is a contraindication to administration of IXIARO.
- WARNINGS AND PRECAUTIONS
  - IXIARO contains protamine sulfate, a compound known to cause hypersensitivity reactions in some individuals.

A Single Dose of Vero Cell–Derived Japanese Encephalitis (JE) Vaccine (Ixiaro) Effectively Boosts Immunity in Travelers Primed With Mouse Brain–Derived JE Vaccines

Erra, et al. Clin Infect Dis. 2012 September 15; 55(6): 825–834.

	Response Rate After 1 Dose of JE-VC[a]		Protection Rate After 1 Dose of JE-VC[b]		Geometric Mean Titers After 1 Dose of JE-VC[b]	
	Nonprimed	Primed	Nonprimed	Primed	Nonprimed	Primed
PRNT Nakayama	39% (10/26)	98% (41/42)	40% (10/25)	100% (17/17)	<10	236
PRNT SA14-14-2	42% (11/26)	95% (40/42)	40% (10/25)	100% (17/17)	12	236

Table 4
Subgroup Analysis of Response Rates, Protection Rates, and Geometric Mean Titers After a Single Dose of Vero Cell–Derived Japanese Encephalitis Vaccine in Previously Primed (Group MB-VC) and Nonprimed (Group VC) Travelers

IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed)
Suspension for Intramuscular Injection
Initial U.S. Approval: 2009

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IXIARO is a vaccine indicated for the prevention of disease caused by Japanese encephalitis virus (JEV). IXIARO is approved for use in individuals 2 months of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration only.

2.1 Dosage and Schedule

Primary Series:

Children 2 months to <3 years of age: Primary immunization with IXIARO consists of two (2) 0.25 mL doses, administered 28 days apart.

Individuals 3 years of age and older: Primary immunization with IXIARO consists of two (2) 0.5 mL doses, administered 28 days apart.

Complete the primary immunization series at least 1 week prior to potential exposure to JEV.

Booster Dose:

Individuals 17 years of age and older: If the primary series of two doses was completed more than 1 year previously, a booster dose may be given if ongoing exposure or re-exposure to JEV is expected.

Infants, children and adolescents 2 months to <17 years of age: The safety and immunogenicity of a booster dose has not been evaluated.

"**Risk determination, therefore, must take into account human activities and the proximity of high-risk areas rather than broad geographic risk determinations**. The following guidelines should be used for administration of the JE vaccine:

1. Individuals **deploying to areas in Pacific Command (PACOM)** should be administered the JE vaccine in accordance with the latest **PACOM Force Health Protection Guidance.**

2. **We advise and highly recommend JE vaccine for Service members, Department of Defense civilians, and beneficiaries who are, or will be, stationed or visiting for more than 30 days in endemic areas**. This includes those who would be based in urban areas, but likely to visit endemic rural or agricultural areas during a high-risk period of JE transmission. Administer booster dose after 1 year according to the ACIP recommendations if risk of exposure continues. Timing of additional booster doses has not yet been determined."

THE ASSIST ANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

MAY 07 2013

"3. We advise recommendation of JE vaccine for the following Service members and beneficiaries:

- Short-term (<1 month) travelers to endemic areas during the JE transmission season if they plan to travel outside of an urban area and have an increased risk for JE exposure.
  1. spending substantial time outdoors in rural or agricultural areas, especially during the evening or night;
  2. participating in extensive outdoor activities (e.g., camping, hiking, trekking, biking, fishing, hunting, or farming); and
  3. staying in accommodations without A/C, screens, bed nets.
- Travelers to an area with an ongoing JE outbreak;
- Travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel; and
- Laboratory workers with potential exposure to infectious JE virus."

Question

- A 52-year-old female had malaise and rash after a 9-day business trip to Jakarta, Indonesia; she is an ex-pat living in Australia. Symptoms included fatigue and non-specific malaise, followed by headache. On day 4, a maculopapular rash developed (trunk, back, and limbs). The rash was accompanied by generalized myalgia, some loose bowel movements, and an occasional dry cough. She did not develop sweats or rigors. Examination on day 5 showed mild bilateral conjunctivitis, rash, but no lymphadenopathy or tenosynovitis. You treat her symptoms. During a follow up visit on day 7 she reports her husband has become ill with a similar syndrome.

- What is your leading differential diagnosis?
  - A. Dengue
  - B. Chikungunya
  - C. Ross River
  - D. Zika virus
  - E. Leptospirosis

Arboviruses

- Family Flaviviridae
  - Genus Flavivirus (53 species, examples below)
    - Dengue, Japanese encephalitis, Kyasanur Forest disease, MVE, Omsk hemorrhagic fever, Powassan, Rio Bravo, SLE, TBE, WNV, Yellow fever, **Zika virus**
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    - Pegivurs A, Pegivurs B
  - Genus Pestivirus (4 species)
    - Border disease virus, Bovine viral diarrheal virus 1, Bovine diarrheal virus 2, Classical swine fever virus

Zika Virus

- Flavivirus (family Flaviviridae)
- Isolated in 1948 from a rhesus monkey
  - Zika forest, near Entebbe, Uganda
- Serologic evidence of human infection in Africa and Asia
- Transmitted to humans by infected mosquitoes
  - *Aedes africanus, luteocephalus, aegypti, others*
- Yap Island outbreak (2007) the first outside Asia, Africa
- Human to human transmission suspected

Zika Virus

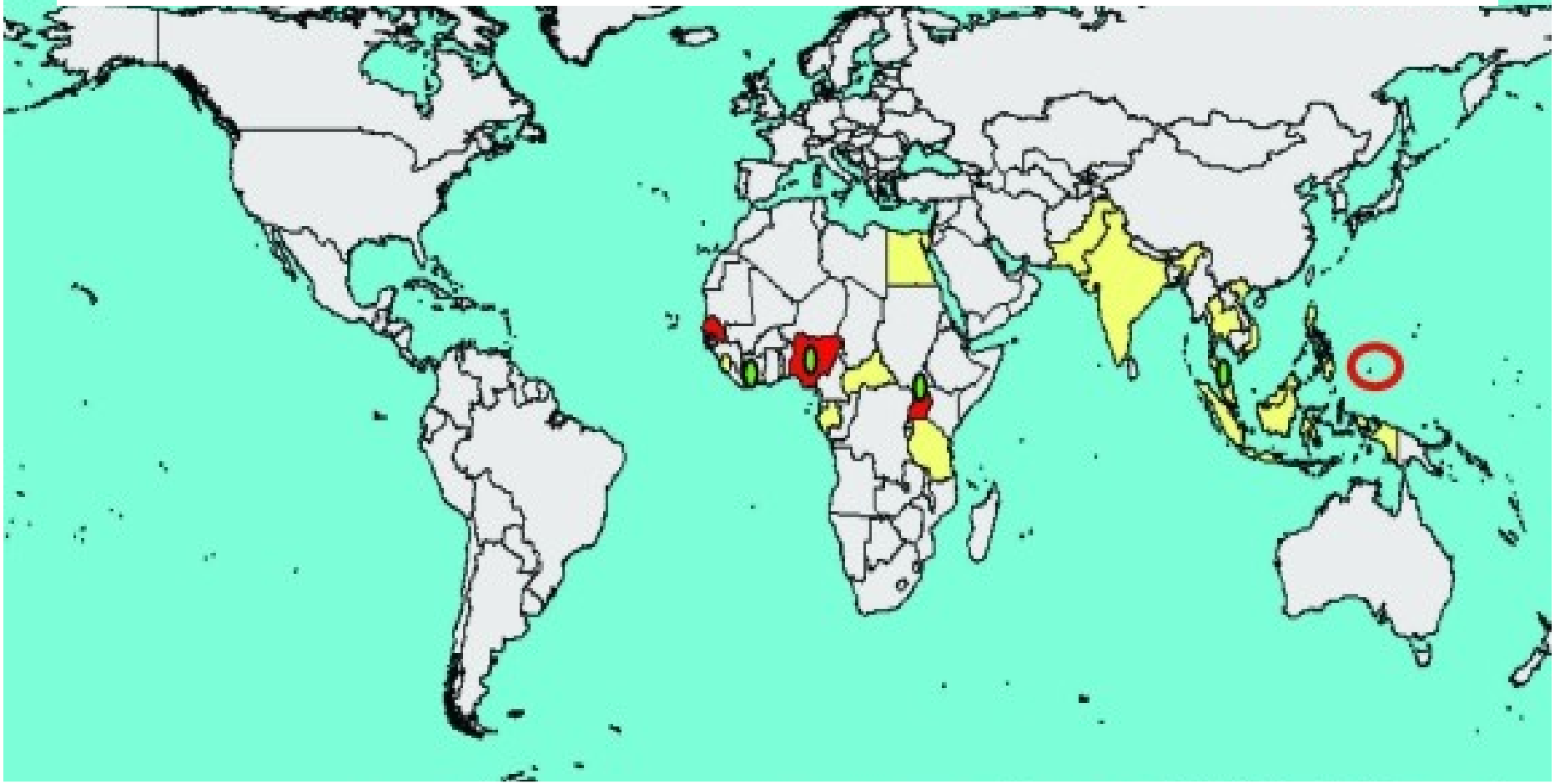


Figure 1 Approximate known distribution of Zika virus, 1947–2007. Red circle represents Yap Island. Yellow indicates human serologic evidence; red indicates virus isolated from humans; green represents mosquito isolates.

Table 1. Clinical Characteristics of 31 Patients with Confirmed Zika Virus Disease on Yap Island during the Period from April through July 2007.

Sign or Symptom	No. of Patients (%)
Macular or papular rash	28 (90)
Fever*	20 (65)
Arthritis or arthralgia	20 (65)
Nonpurulent conjunctivitis	17 (55)
Myalgia	15 (48)
Headache	14 (45)
Retro-orbital pain	12 (39)
Edema	6 (19)
Vomiting	3 (10)

* Cases of measured and subjective fever are included.

Table. Reported or observed clinical signs and symptoms in persons with Zika virus infection, 1962–2010

	Country, year of infection origin,* no. (%) patients					
Sign or symptom	Uganda, 1962, n = 1	Laboratory acquired, 1973, n = 1	Indonesia, 1977–1978, n = 7	Micronesia, 2007, n = 28	Senegal/United States, 2009, n = 3	Cambodia, 2010, n = 1
Fever	1 (100)	1 (100)	7 (100)	20 (65)		1 (100)
Headache	1 (100)			14 (45)	3 (100)	1 (100)
Malaise	1 (100)		5 (71)		3 (100)	
Maculopapular rash	1 (100)			28 (100)	3 (100)	
Fatigue or myalgia	1 (100)	1 (100)	1 (14)	14 (45)	1 (33)	
Arthritis and arthralgia			1 (14)	20 (65)	3 (100)	
Chills		1 (100)	2 (29)		2 (67)	
Dizziness			5 (71)			
Joint swelling or edema				6 (19)	2 (67)	
Stomachache			6 (86)			
Retro-orbital pain		1 (100)		12 (39)		
Conjunctivitis			1 (14)	17 (55)	1 (33)	
Anorexia			4 (57)			
Photophobia					1 (33)	
Vomiting			1 (14)	3 (10)		
Diarrhea			3 (43)			
Constipation			3 (43)			
Sore throat						1 (100)
Cough						1 (100)
Aphthous ulcer					2 (67)	
Hypotension			2 (29)			
Hematuria			1 (14)			
Prostatitis					1 (33)	
Hematospermia					1 (33)	
Sweating		1 (100)				
Lightheadedness					1 (33)	

*References: Uganda (*2*), laboratory-acquired (*10*), Indonesia (*5*), Micronesia (*9*), Senegal/United States (*4*). Blank cells indicate no reported information.

Probable Non–Vector-borne Transmission of Zika Virus, Colorado, USA

Brian D. Foy, Kevin C. Kobylinski, Joy L. Chilson Foy, Bradley J. Blitvich,
Amelia Travassos da Rosa, Andrew D. Haddow, Robert S. Lanciotti, and Robert B. Tesh

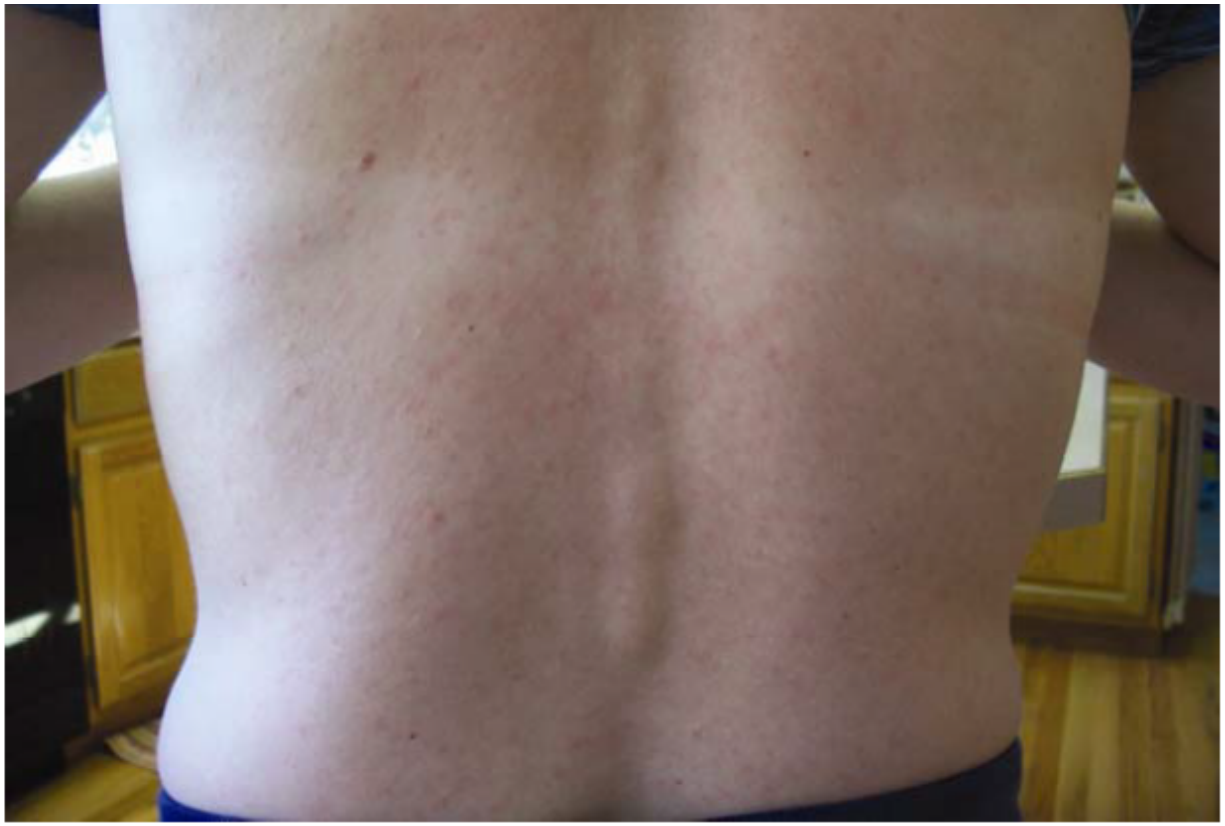


Figure. Maculopapular rash on patient 3 infected with Zika virus, Colorado, USA.

Zika Virus

- Diagnosis
  - Travel to known area of transmission
  - Compatible clinical syndrome
  - Serology (cross reactivity with dengue)
    - IgM ELISA
    - Neutralizing antibodies
  - Molecular
    - RT-PCR
    - Sequencing

Zika Virus

- Prevention
  - No vaccine or prophlyactic drug
  - PPMs and vector avoidance

- Treatment
  - Supportive
  - Close resemblance to dengue on presentation likely warrants avoidance of NSAIDS and aspirin until Dx
  - Case report of possible human to human transmission requires counseling

Arboviruses

- Family Bunyaviridae
  - Genus Nairovirus
    - Crimean–Congo hemorrhagic fever virus (CCHF)
  - Genus Orthobunyavirus
    - California encephalitis virus
    - La Crosse encephalitis virus (LACV)
    - Bunyamwera virus
  - Genus Phlebovirus
    - Rift Valley fever virus (RVFV)
    - Toscana virus (TOSV)

Arboviruses

- Family Reoviridae
  - Subfamily Sedoreovirinae
    - Genus Orbivirus
      - African horse sickness virus (AHSV)
      - Bluetongue disease virus (BTV)
      - Equine encephalosis virus (EEV)
    - Genus Seadornavirus
      - Banna virus (BAV)
  - Subfamily Spinareovirinae
    - Genus Coltivirus
      - Colorado tick fever virus (CTFV)

Arboviruses

- Family Picornaviridae
  - Genus Parechovirus
    - Sebokele virus 1

Summary

- Arboviral diseases are pervasive and difficult to prevent

- Clinical syndromes overlap across viruses
  - RRV: constitutional symptoms, rash, joints
  - CHIK: constitutional symptoms, joint / tendon, chronic
  - ZIKA: constitutional symptoms, rash, conjunctivitis
  - JE: vaccine preventable disease, high morbid/mortality
  - YF: vaccine preventable, potential for severe Aes
  - DEN: most important arbovirus see other lecture

- Prevention and treatment
  - Know geographic distribution, PMMs, vaccinate (JE/YF)
  - Symptomatic treatment, avoid platelet modifying drugs

Questions?

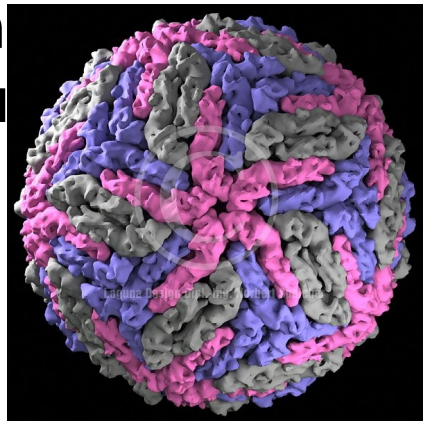
Question #3

- 18 year old native from Thailand (moved to US at 10 years of age) presents on day 2 of illness with fever, headache, eye pain, bone pain, and nausea 3 days after returning from a vacation in Puerto Rico. Dengue is suspected and he is treated symptomatically as an outpatient with NSAIDS and po fluid intake is encouraged. He returns day 6 of his illness afebrile with resolution of some symptoms but he now has abdominal pain, slight shortness of breath, and some confusion.

- What is the best next step and rationale for the same?
  - A. Continue close follow up as outpatient, encourage po fluid intake, this is the natural history of a resolving dengue infection
  - B. Admit to the hospital, approach as a critically ill patient, this is a severe dengue virus infection
  - C. Admit to the hospital, evaluate for another infectious disease process, these new symptoms represent a new medical problem
  - D. Prescribe doxycycline, he probably has leptospirosis

Arboviruses

- Family Flaviviridae
  - Genus Flavivirus (53 species, examples below)
    - **Dengue**, Japanese encephalitis, Kyasanur Forest disease, MVE, Omsk hemorrhagic fever, Powassan, Rio Bra SLE, TBE, WNV, Yellow fever, Zika viru
  - Genus Hepacivirus (1 species)
    - Hepatitis C virus
  - Genus Pegivirus (2 species)
    - Pegivurs A, Pegivurs B
  - Genus Pestivirus (4 species)
    - Border disease virus, Bovine viral diarrheal virus 1, Bovine diarrheal virus 2, Classical swine fever virus



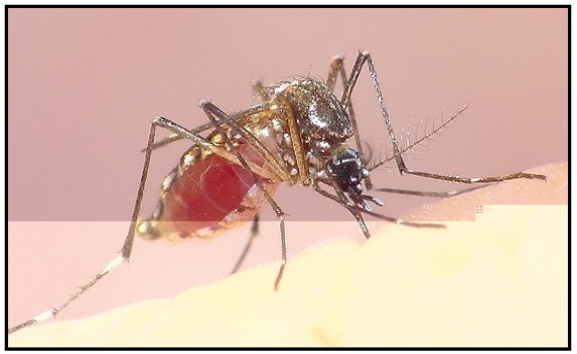
Dengue

Dengue Virus (DENV)

- Virus
  - Flavivirus (YF, JE, WNV, DENV)
  - 4 dengue virus types: DENV-1-4
    - Multiple genotypes within each dengue virus type

- Vector
  - Mosquito (*Aedes aegypti / albopictus*)

- Transmission
  - Feeding mosquito vector
  - Laboratory
  - Blood supply?



Aedes aegypti

Dengue Burden

Under-estimated and under-reported

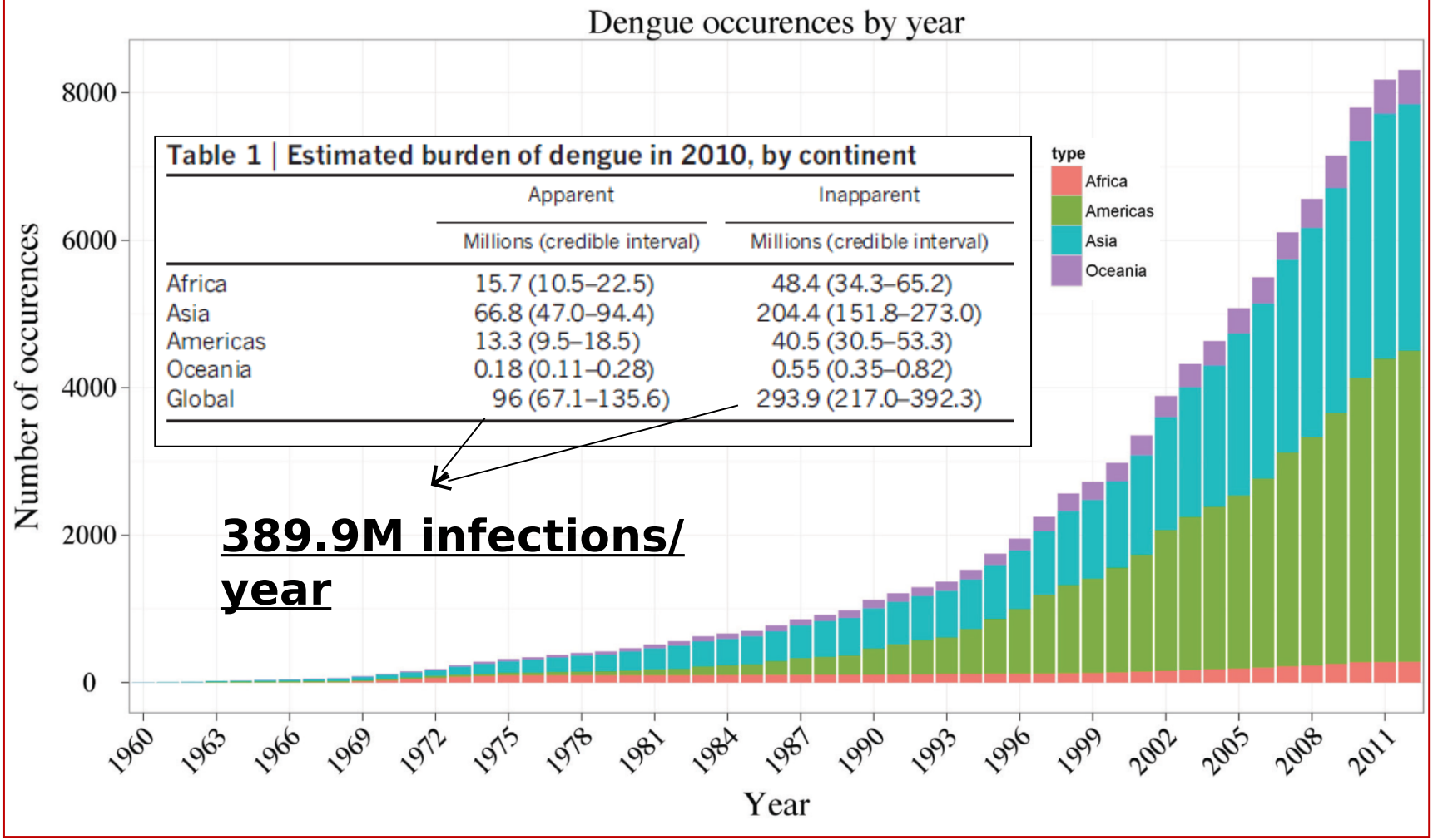


Table 1 | Estimated burden of dengue in 2010, by continent

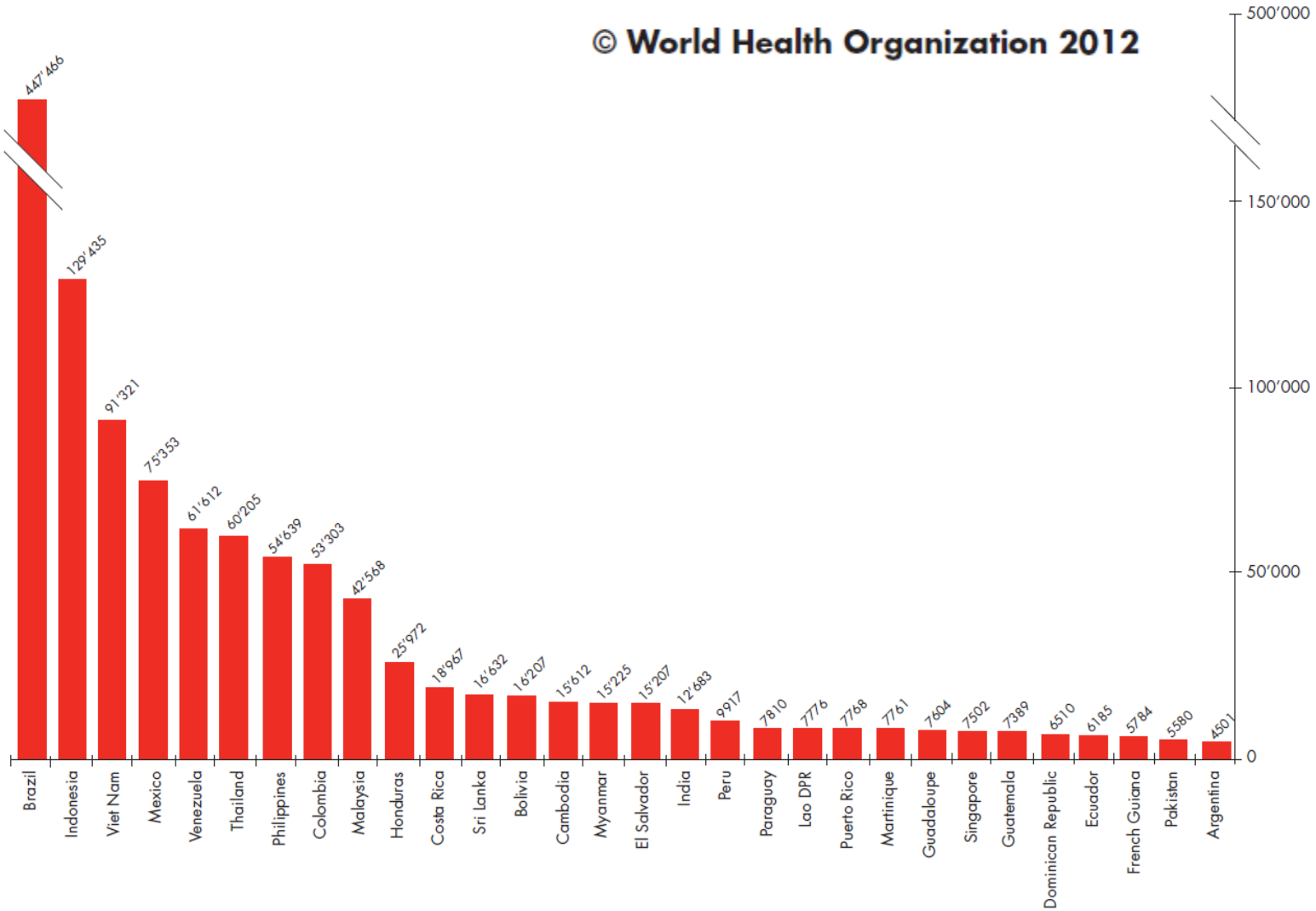
	Apparent	Inapparent
	Millions (credible interval)	Millions (credible interval)
Africa	15.7 (10.5–22.5)	48.4 (34.3–65.2)
Asia	66.8 (47.0–94.4)	204.4 (151.8–273.0)
Americas	13.3 (9.5–18.5)	40.5 (30.5–53.3)
Oceania	0.18 (0.11–0.28)	0.55 (0.35–0.82)
Global	96 (67.1–135.6)	293.9 (217.0–392.3)

389.9M infections/ year

Bhatt et al., Nature. 2013 Apr 7.

GLOBAL STRATEGY FOR DENGUE PREVENTION AND CONTROL

Figure 3. Average number of dengue cases in 30 most highly endemic countries/territories as reported to WHO, 2004–2010



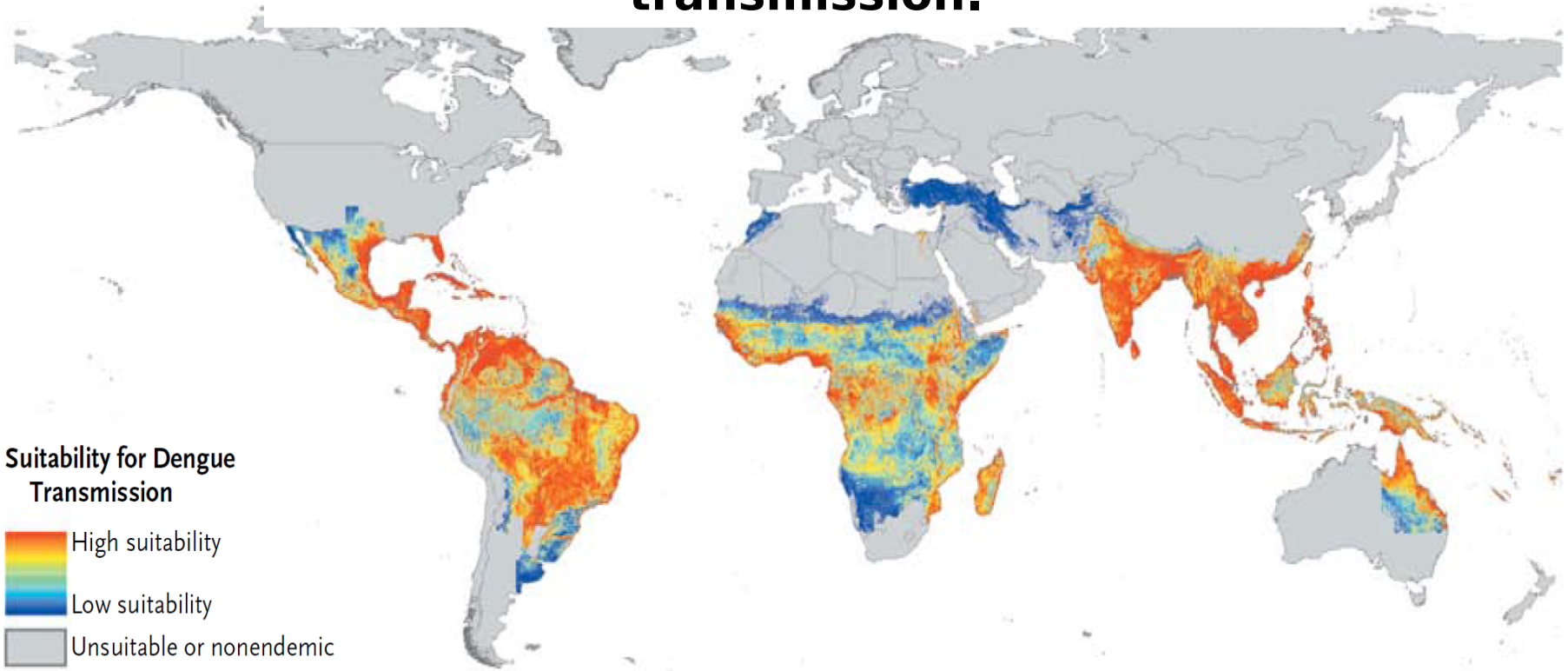
CURRENT CONCEPTS

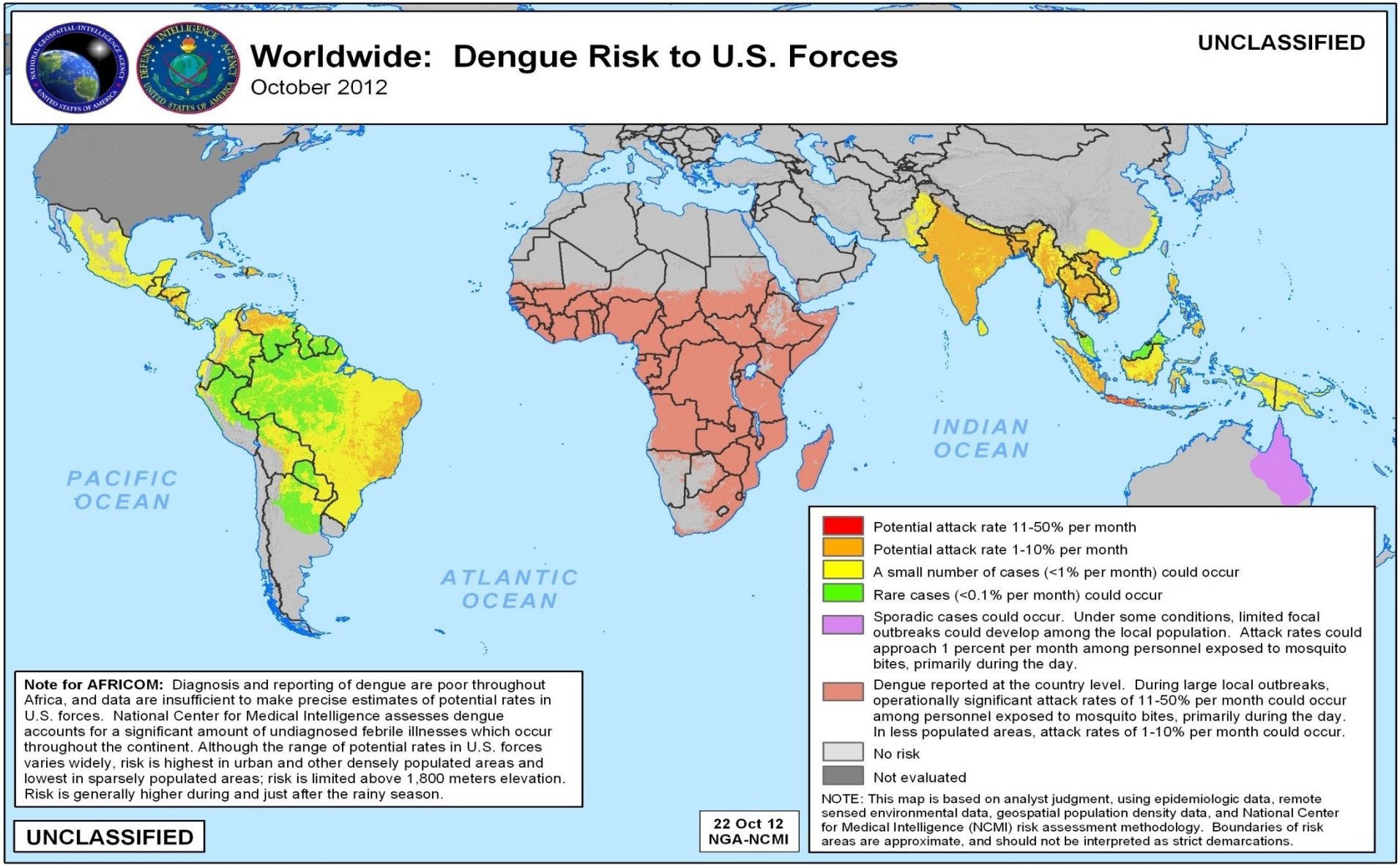
Dengue

Cameron P. Simmons, Ph.D., Jeremy J. Farrar, M.D., Ph.D.,
Nguyen van Vinh Chau, M.D., Ph.D., and Bridget Wills, M.D., D.M.

N Engl J Med 2012;366:1423-32.

Areas supporting dengue virus transmission.



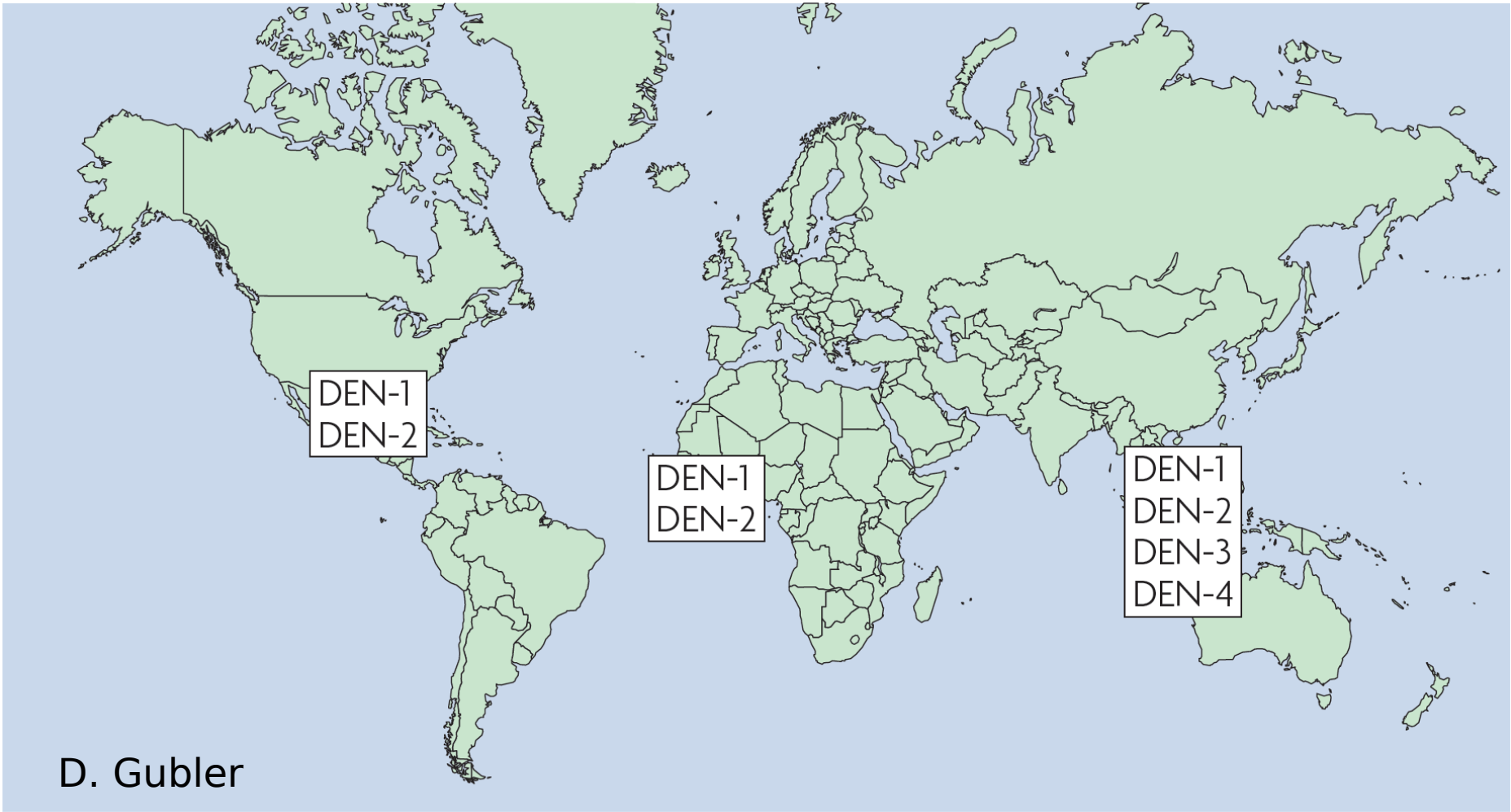

Worldwide: Dengue Risk to U.S. Forces
October 2012
UNCLASSIFIED
PACIFIC OCEAN
ATLANTIC OCEAN
INDIAN OCEAN
Potential attack rate 11-50% per month
Potential attack rate 1-10% per month
A small number of cases (<1% per month) could occur
Rare cases (<0.1% per month) could occur
Sporadic cases could occur. Under some conditions, limited focal outbreaks could develop among the local population. Attack rates could approach 1 percent per month among personnel exposed to mosquito bites, primarily during the day.
Dengue reported at the country level. During large local outbreaks, operationally significant attack rates of 11-50% per month could occur among personnel exposed to mosquito bites, primarily during the day. In less populated areas, attack rates of 1-10% per month could occur.
No risk
Not evaluated
NOTE: This map is based on analyst judgment, using epidemiologic data, remote sensed environmental data, geospatial population density data, and National Center for Medical Intelligence (NCMI) risk assessment methodology. Boundaries of risk areas are approximate, and should not be interpreted as strict demarcations.
Note for AFRICOM: Diagnosis and reporting of dengue are poor throughout Africa, and data are insufficient to make precise estimates of potential rates in U.S. forces. National Center for Medical Intelligence assesses dengue accounts for a significant amount of undiagnosed febrile illnesses which occur throughout the continent. Although the range of potential rates in U.S. forces varies widely, risk is highest in urban and other densely populated areas and lowest in sparsely populated areas; risk is limited above 1,800 meters elevation. Risk is generally higher during and just after the rainy season.
UNCLASSIFIED
22 Oct 12
NGA-NCMI
Datum: WGS84, Coordinate System: World_Robinson
Boundary representation is not necessarily authoritative.

Factors Driving Transmission

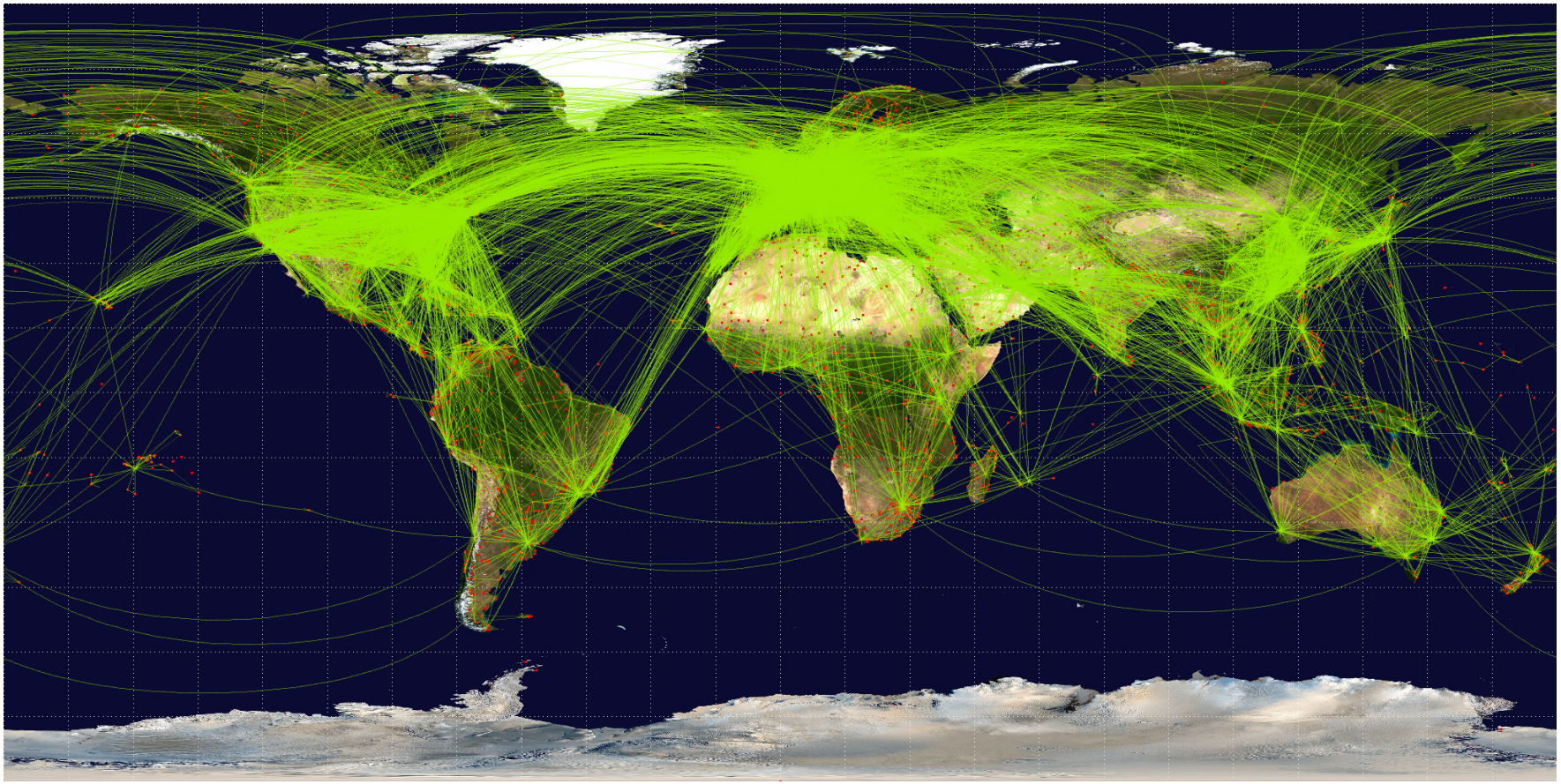
- Population increases
- Migration
- Urbanization
- Poverty
- Vector expansion
- International travel

- Changing global ecology
- Vector evolution
- Viral evolution

DENV Type Distribution - 1970

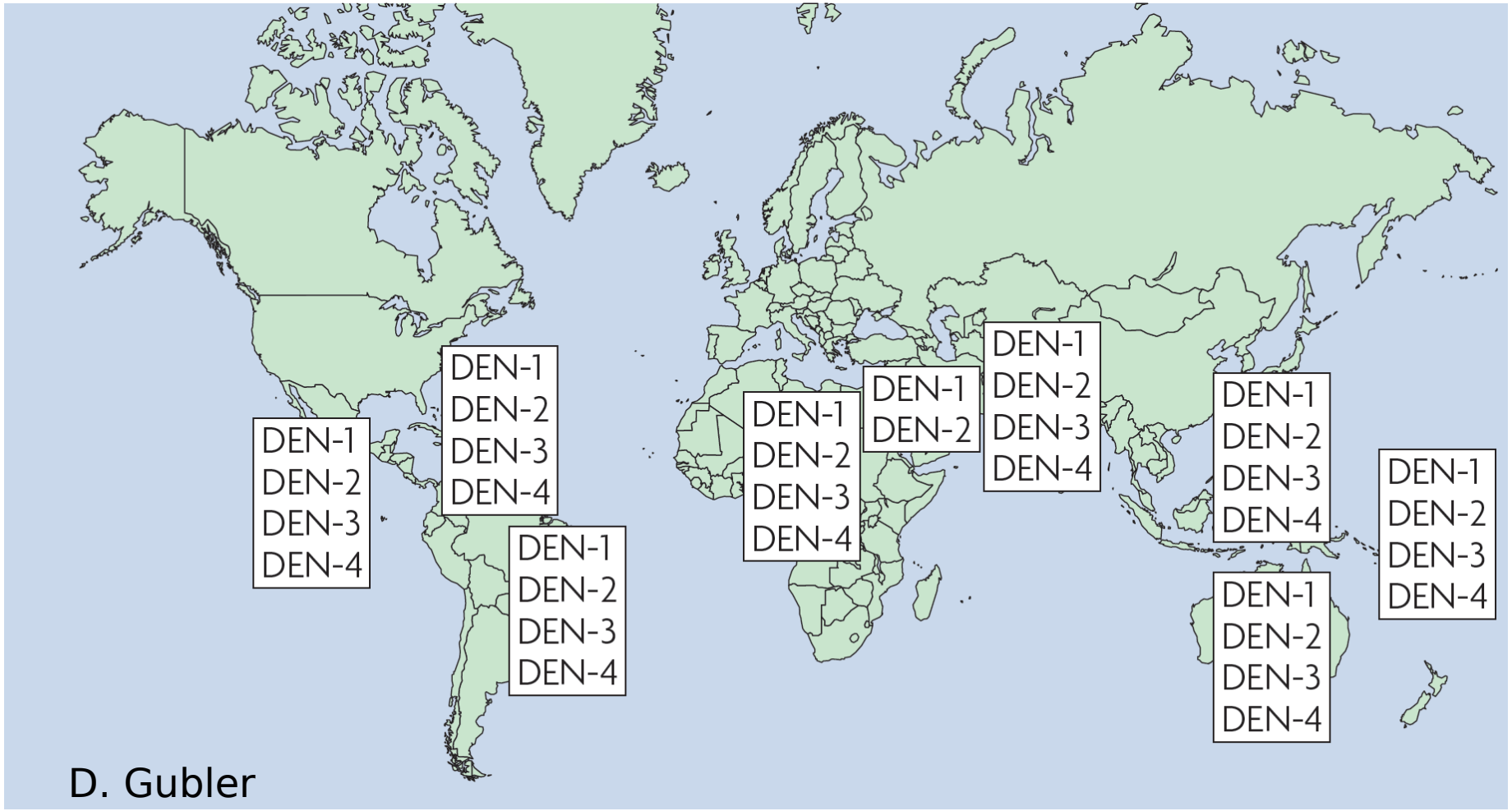


Global Air Travel Flight Patterns



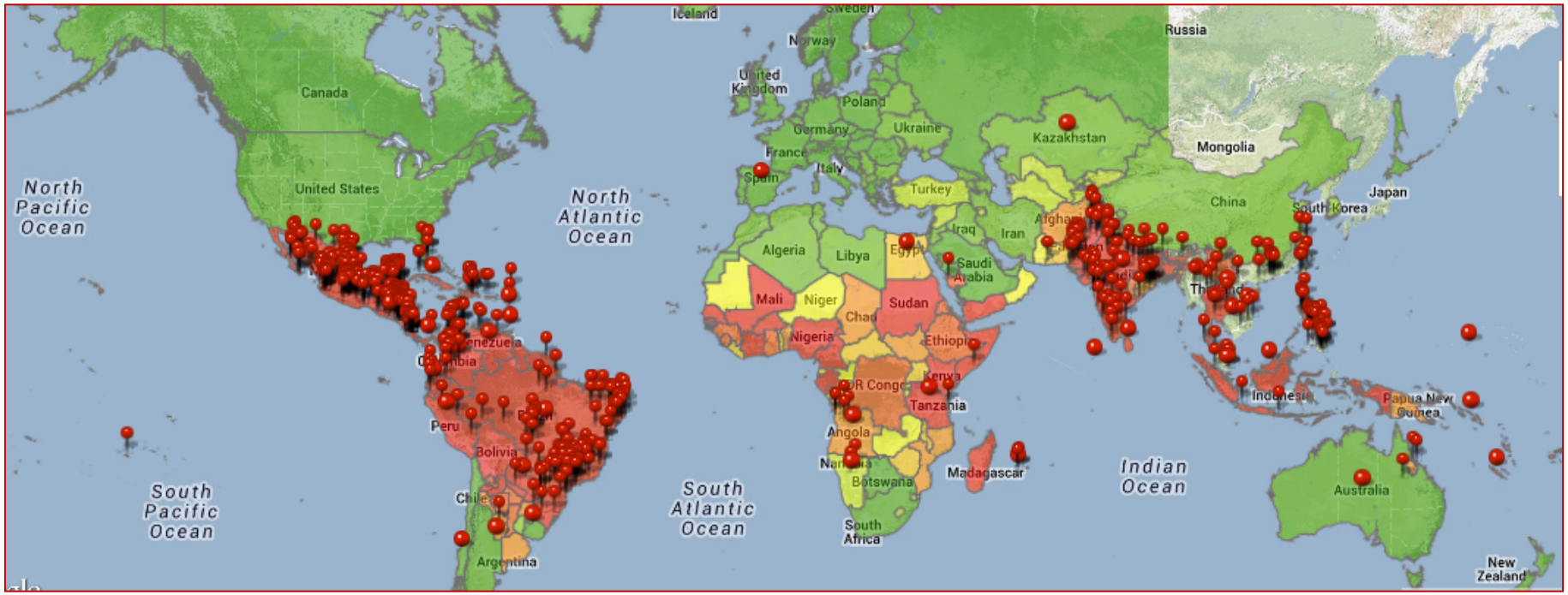
http://upload.wikimedia.org/wikipedia/commons/a/ac/World-airline-routemap-2009.png

DENV Type Distribution - 2004



DengueMap
A CDC-HealthMap Collaboration

10 SEP 2013



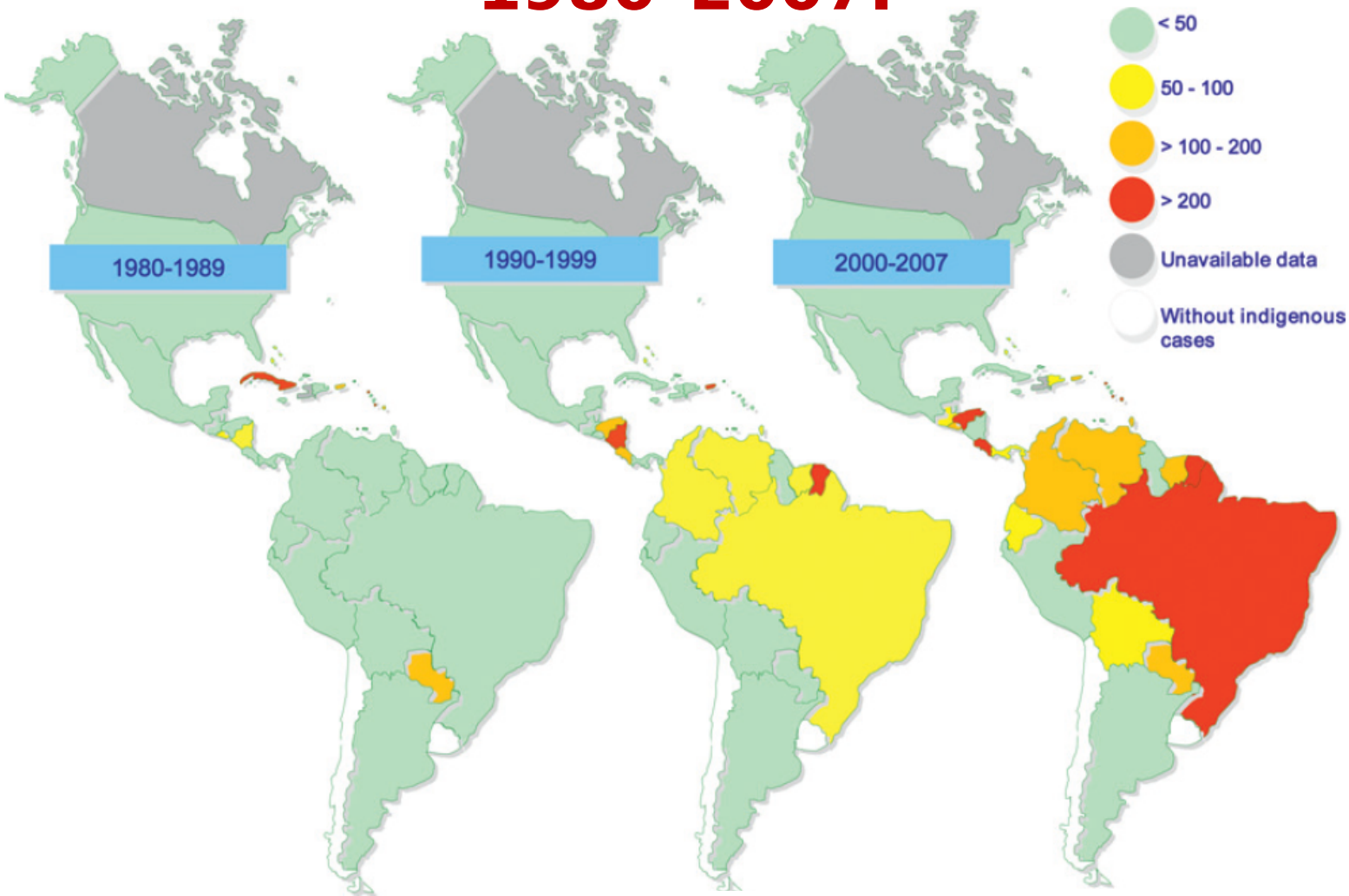
HealthMap Reports: Recent reports of local and regional dengue or imported cases of dengue from official, newspaper, and other media sources. View source »

Country Level Local or Province Level

IDAMS Global Consensus Map: These risk areas are defined based on consensus between a variety of data sources including: national surveillance systems, published literature, questionnaires and formal and informal news reports. View source »

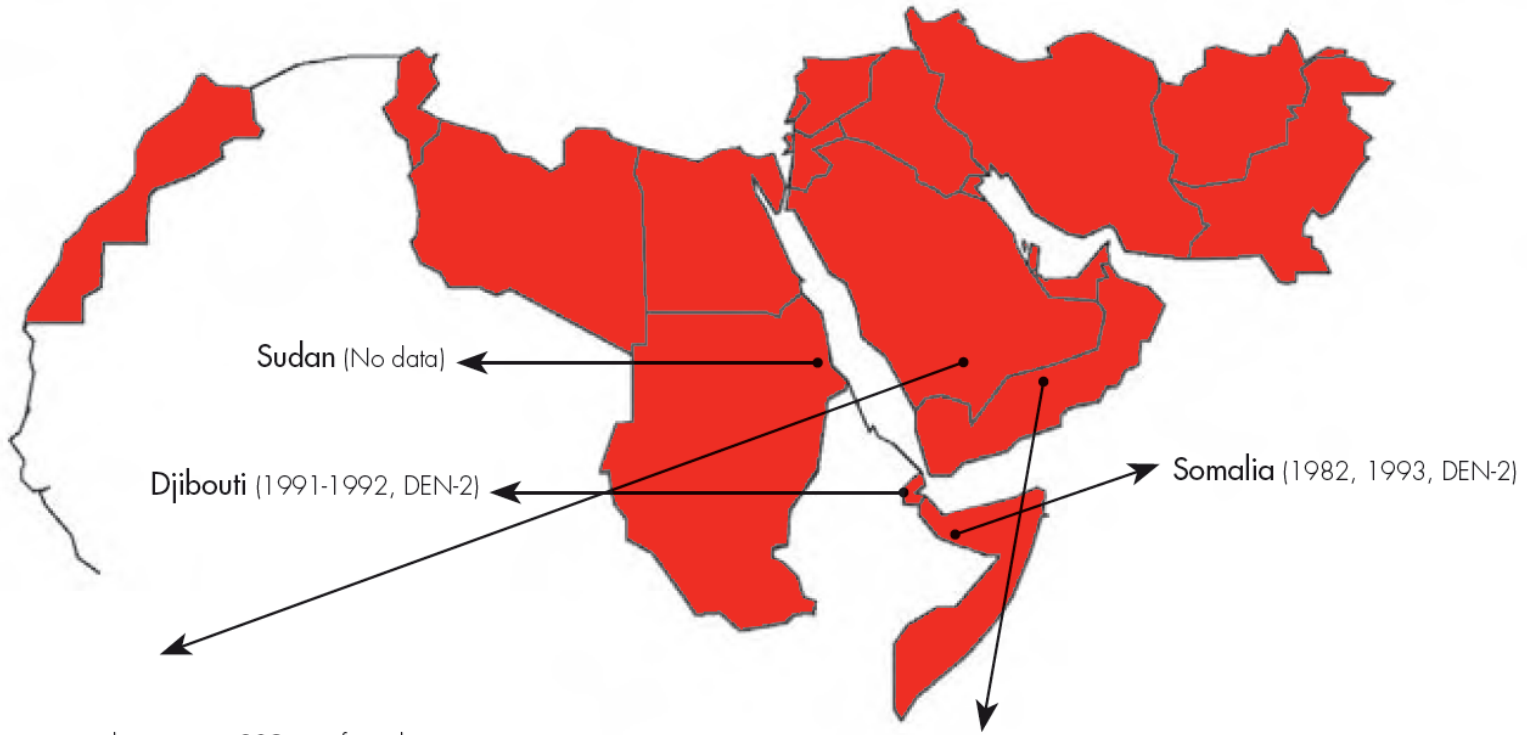
Absent Unlikely Uncertain Likely Present

Average dengue incidence per 100,000 by country, Region of the Americas, 1980–2007.



Am. J. Trop. Med. Hyg., 82(1), 2010, pp. 128–135

Figure 1.3 Outbreaks of dengue fever in the WHO Eastern Mediterranean Region, 1994–2005



DEN-2:

1994:	673	suspected cases,	289	confirmed cases
1995:	136	suspected cases,	6	confirmed cases
1996:	57	suspected cases,	2	confirmed cases
1997:	62	suspected cases,	15	confirmed cases
1998:	31	suspected cases,	0	confirmed cases
1999:	26	suspected cases,	3	confirmed cases
2000:	17	suspected cases,	0	confirmed cases
2001:	7	suspected cases,	0	confirmed cases
2005:	32	suspected (confirmed)		

Al-Hudaydah, Mukkala, Shaabwa
(1994, DEN-3, no data);

Al-Hudaydah, Yemen
(September 2000, DEN-2, 653 suspected cases, 80 deaths (CFR = 12%));

Al-Hudaydah, Yemen
(March 2004, 45 suspected cases, 2 deaths);

Al-Hudaydah, Mukkala
(March 2005, 403 suspected cases, 2 deaths);

Pakistan

DENGUE FEVER CASES SUMMARY REPORTS
13 October 2011 (02:00 pm)

Dengue cases	Total
No. of suspected cases	286,857
No. of confirmed cases	16,288
No. of admitted cases	1,353
No. of cured cases	16,066
No. of reported Deaths	217

Dengue Virus Infection in Africa

Ananda Amarasinghe, Joel N. Kuritsky, G. William Letson, and Harold S. Margolis

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 8, August 2011

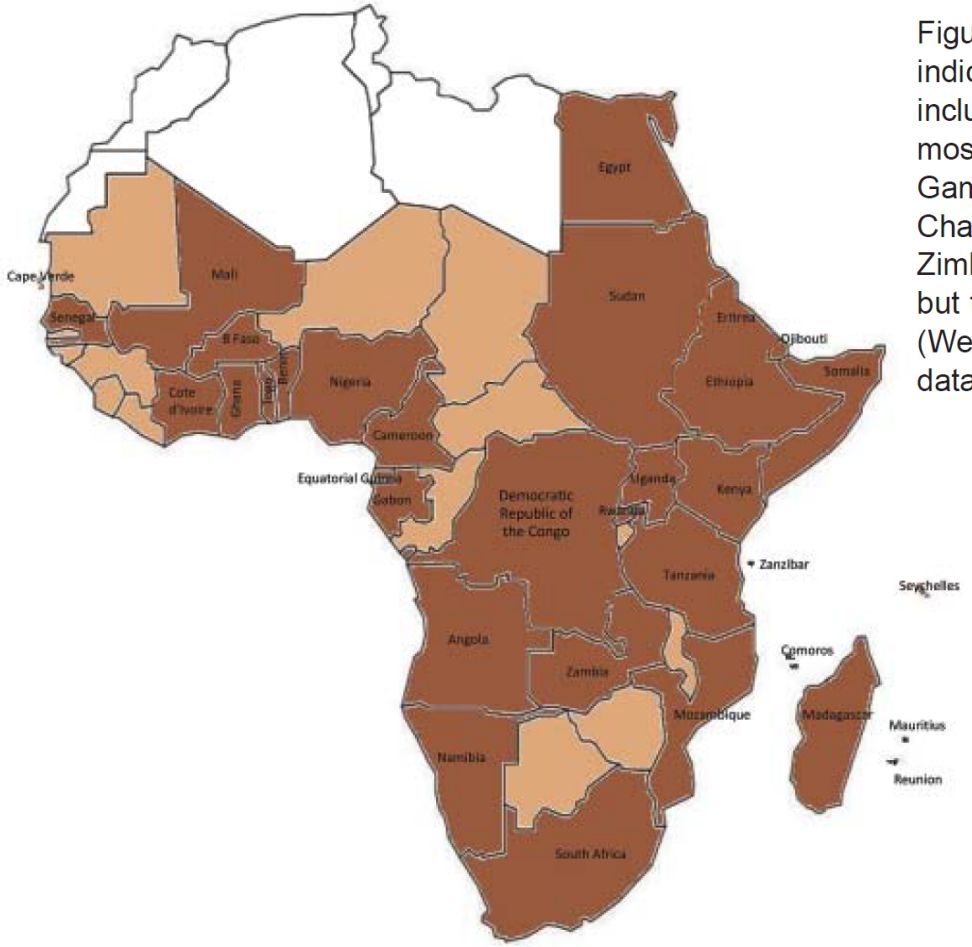


Figure. Dengue and *Aedes aegypti* mosquitoes in Africa. Brown indicates 34 countries in which dengue has been reported, including dengue reported only in travelers, and *Ae. aegypti* mosquitoes. Light brown indicates 13 countries (Mauritania, The Gambia, Guinea-Bissau, Guinea, Sierra Leone, Liberia, Niger, Chad, Central African Republic, Republic of the Congo, Malawi, Zimbabwe, and Botswana) in which dengue has not been reported but that have *Ae. aegypti* mosquitoes. White indicates 5 countries (Western Sahara, Morocco, Algeria, Tunisia, and Libya) for which data for dengue and *Ae. aegypti* mosquitoes are not available.

Brown – dengue reported

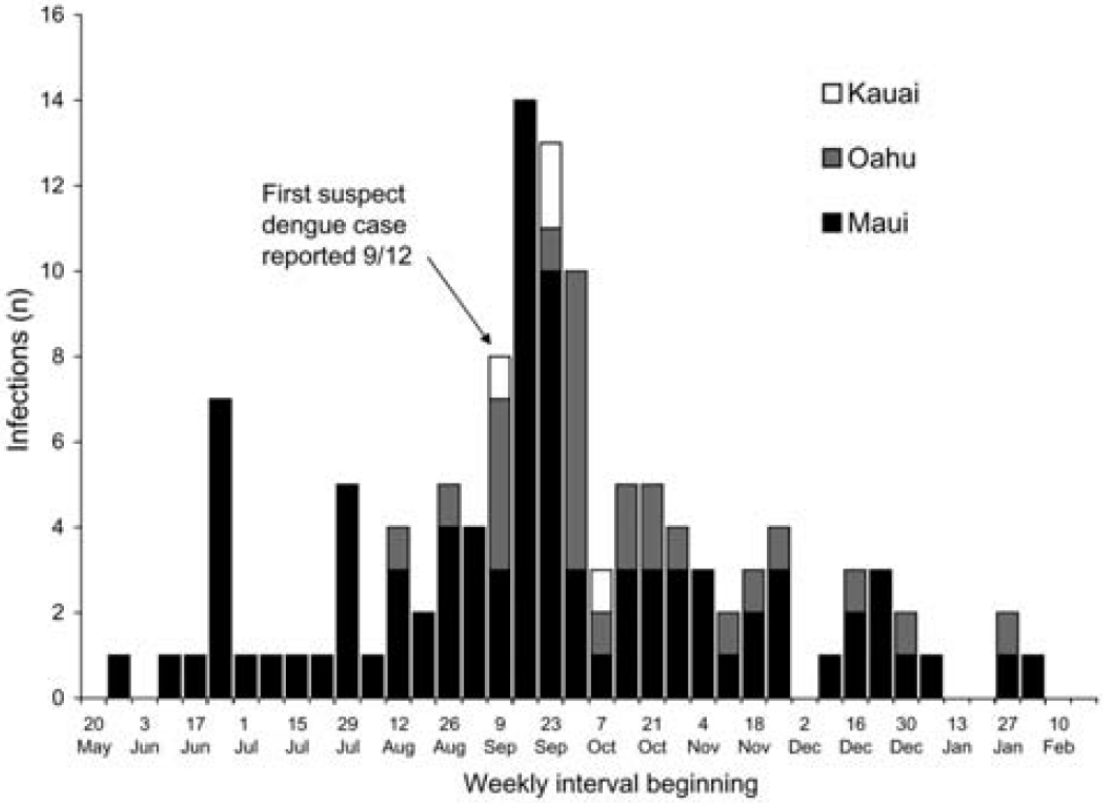
Light Brown – dengue not reported but vector exists

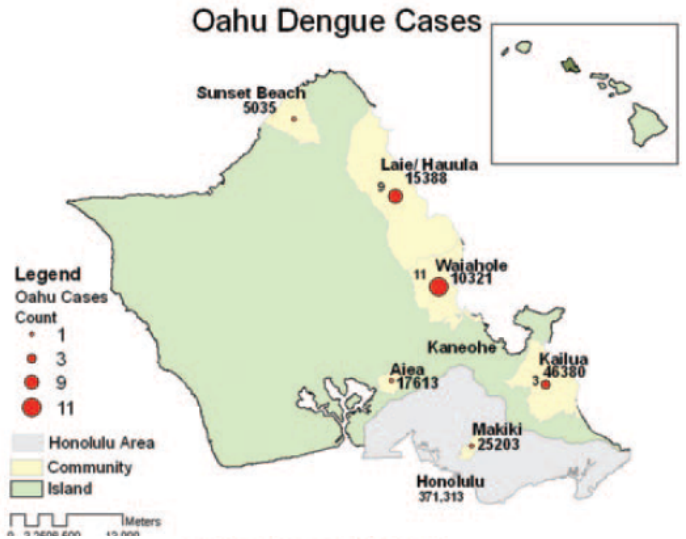
White – data not available

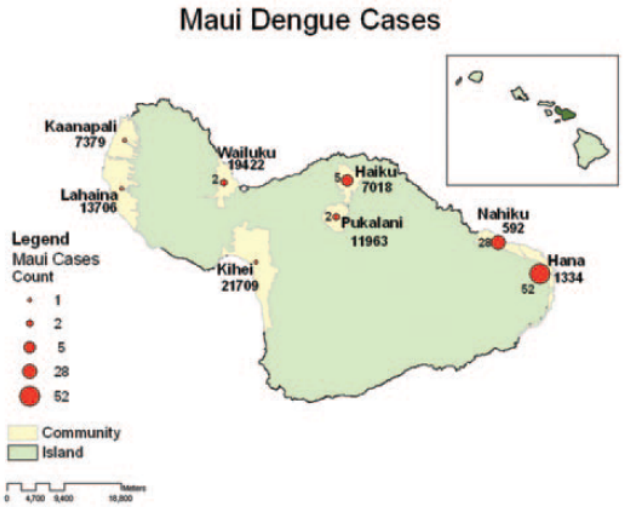
Dengue Fever, Hawaii, 2001–2002

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 11, No. 5, May 2005

Paul V. Effler,* Lorrin Pang,* Paul Kitsutani,† Vance Vorndam,† Michele Nakata,* Tracy Ayers,*
Joe Elm,* Tammy Tom,* Paul Reiter,† José G. Rigau-Perez,† John M. Hayes,† Kristin Mills,*
Mike Napier,‡ Gary G. Clark,† and Duane J. Gubler*
for the Hawaii Dengue Outbreak Investigation Team[1]







Am. J. Trop. Med. Hyg., 59(1), 1998, pp. 95–99

DENGUE SURVEILLANCE IN TEXAS, 1995

JULIE A. RAWLINGS, KATHERINE A. HENDRICKS, CHRISTINE R. BURGESS, RICHARD M. CAMPMAN, GARY G. CLARK, LAURA J. TABONY, AND MARY ANN PATTERSON

Infectious Disease Epidemiology and Surveillance Division and Bureau of Laboratories, Texas Department of Health, Austin, Texas; Dengue Branch, Centers for Disease Control and Prevention, San Juan, Puerto, Rico

Dengue Hemorrhagic Fever --- U.S.-Mexico Border, 2005

MMWR Weekly
August 10, 2007 / 56(31);785-789

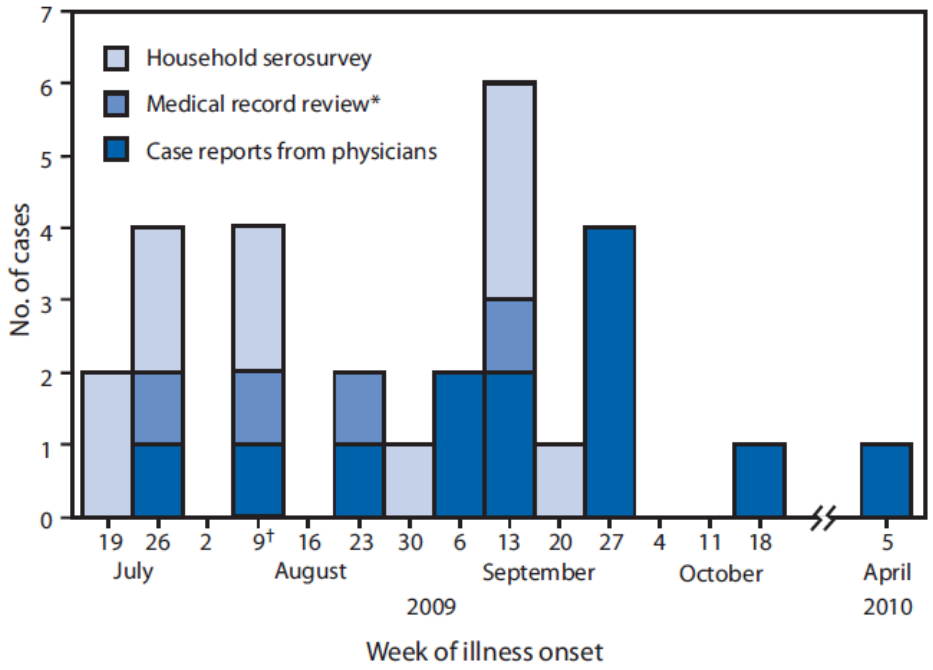
Am. J. Trop. Med. Hyg., 78(3), 2008, pp. 364–369

Epidemic Dengue and Dengue Hemorrhagic Fever at the Texas–Mexico Border: Results of a Household-based Seroepidemiologic Survey, December 2005

Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
Weekly / Vol. 59 / No. 19 May 21, 2010

Locally Acquired Dengue — Key West, Florida, 2009–2010

FIGURE. Number of locally acquired dengue cases (N = 28), by week of illness onset and method of identification — Key West, Florida, 2009–2010



*Two cases identified in both household serosurvey and medical record review are shown as record review cases.
†Week of illness onset in index patient.

TABLE. Characteristics of patients (N = 28) with locally acquired dengue — Key West, Florida, 2009–2010

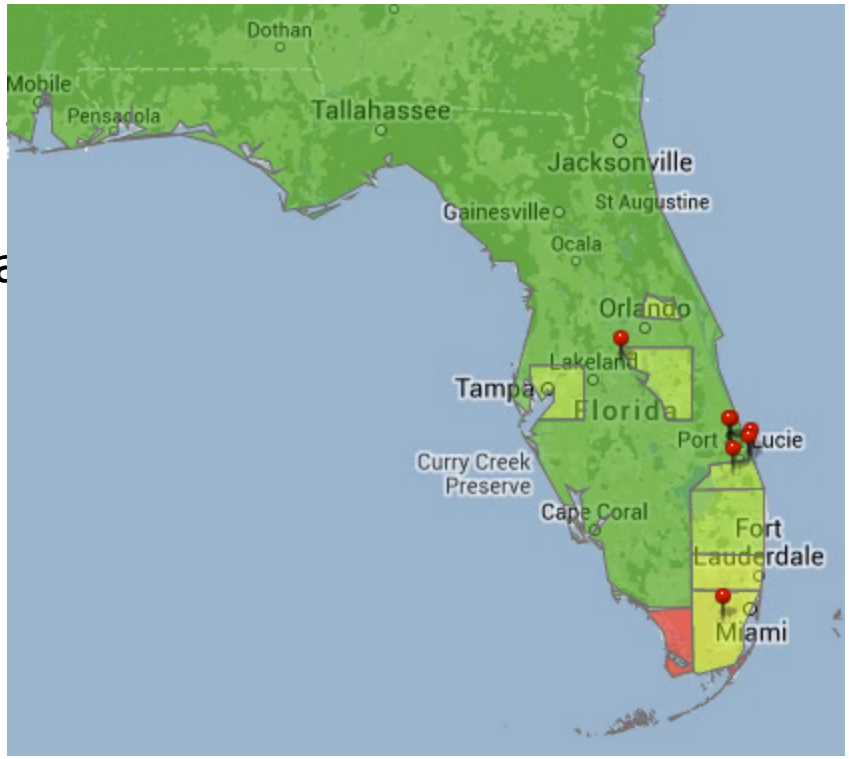
Characteristic	No.	(%)*
Sex		
Male	19	(68)
Female	9	(32)
Age group (yrs)		
<20	1	(4)
21–40	11	(39)
41–60	11	(39)
>60	5	(18)
Race		
White	24	(86)
Black	3	(11)
Asian/Pacific Islander	1	(4)
Ethnicity		
Non-Hispanic	25	(89)
Hispanic	3	(11)
Symptoms		
Fever	28	(100)
Headache	22	(79)
Myalgia	23	(82)
Arthralgia	18	(64)
Eye pain	14	(50)
Rash	15	(54)
Bleeding	6	(21)

*Percentages might not add to 100% because of rounding.

Background: Domestic Risk, Florida

- Locally Acquired Dengue as of SEP 2013:
  - 22 cases
  - 20 residents, 2 out of state
  - Martin (21) and Miami-Dade (
- Imported (traveler) Dengue 2013:
  - 88 cases imported into Florida
- 69 / 110 cases serotyped by PCR

Serotype	# of cases
DENV-1	50
DENV-2	1
DENV-3	3
DENV-4	16
2013 total	69



CDC Dengue Map, 15 OCT 2013

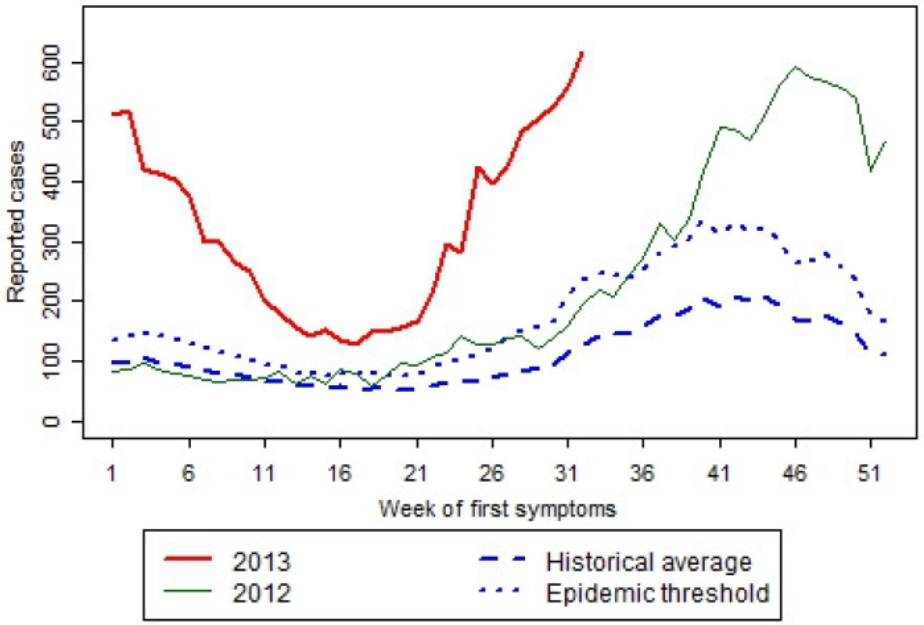
References: 5) Florida Dept. of Health Website 6) *Florida Arbovirus Surveillance:* Week 36 September 2013

Background: Domestic Risk

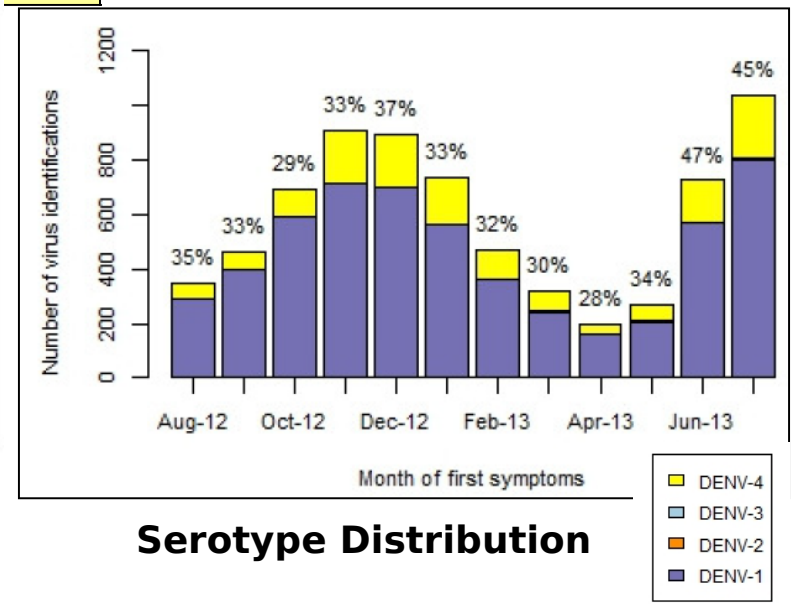
- Indigenous transmission: Florida (2013), Texas (Houston), Hawaii
- U.S. Territories: Puerto Rico, Virgin Islands, Samoa, Guam
- Febrile illnesses in returning traveler: ~100-200 cases per year

Puerto Rico: 2013

Suspected cases reported compared to the historical a



Total viral identifications in the last 12 months



Serotype Distribution

Totals through 17 SEP 2013: 11,141 suspected, 5916 confirmed, 43 severe (DHF), 1 death

References: 1) CDC Website ... 4) *Dengue Surveillance Weekly Report*, CDC, September 2013

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 12, 2006 VOL. 354 NO. 2

Spectrum of Disease and Relation to Place of Exposure among Ill Returned Travelers

David O. Freedman, M.D., Leisa H. Weld, Ph.D., Phyllis E. Kozarsky, M.D., Tamara Fisk, M.D.,* Rachel Robins, M.D., Frank von Sonnenburg, M.D., Jay S. Keystone, M.D., Prativa Pandey, M.D., and Martin S. Cetron, M.D., for the GeoSentinel Surveillance Network†

Table 3. **Etiologic Diagnoses within Selected Syndrome Groups, According to Travel Region.***

Syndrome and Cause	All Regions	Caribbean	Central America	South America	Sub-Saharan Africa	South Central Asia	Southeast Asia	Other or Multiple Regions†
	number of cases per 1000 patients with syndrome							
Systemic febrile illness (n=3907)								
Specific pathogen or cause reported‡	594	459	527	446	718	522	547	454
Malaria‡	352	65	133	133	622	139	130	234
Dengue‡	104	238	123	138	7	142	315	35
Mononucleosis (due to Epstein–Barr virus or cytomegalovirus)‡	32	70	69	79	10	17	32	63
Rickettsial infection‡	31	0	0	0	56	10	16	24
Salmonella typhi or *S. paratyphi* infection‡	29	22	25	17	7	141	26	24
No specific cause reported‡	406	541	473	554	282	478	453	546

‡ $P<0.01$ for the comparison among regions.

*"With respect to specific diagnoses, malaria was one of the three most frequent causes of systemic febrile illness among travelers from every region, **although travelers from every region except sub-Saharan Africa and Central America had confirmed or probable dengue more frequently than malaria**."*

Dengue Risk / Threat to DoD

- **Prevalence and Risk to Soldiers (2003-2012)**
  - Total Cases: 631
    - Active Duty: 177; Reserve: 35; MHS Beneficiaries: 419
    - No record of attributable deaths
  - Dengue Mission Impact Projections
    - Not severe: hospitalized ~5-7 days, low functioning ~14-28 days
    - Severe: evacuation to MTF, ICU care?, death?, LDD >1 month
  - Deployment
    - DODSR: 500 samples, deployed between 2006-2008
      - 11.2% seroprevalence of dengue antibody
      - 2.4% with monovalent profile (high risk with next infection)

References: *Dengue Tetravalent Vaccine CDD; ⁺DMSS

Seroprevalence of DENV Exposure in Deployed Personnel

- DODSR, 1000 samples, first time deployers, 2008-2011
- 250 samples selected per COCOM
- Tested for presence of neutralizing antibody by microneut assay
- Overall 7.6% seroprevalence rate of past dengue exposure
- 1.5% seroconversion rate during deployment (first infection)
- Increased self report of fever during deployment in those with antibodies

Seroprevalence Based on 1,000 Post-Deployment Samples in First Time Deployers

	Central America	South America	Asia	Africa	Total
Percent	4.8%	12.4%	7.2%	6.0%	7.6%

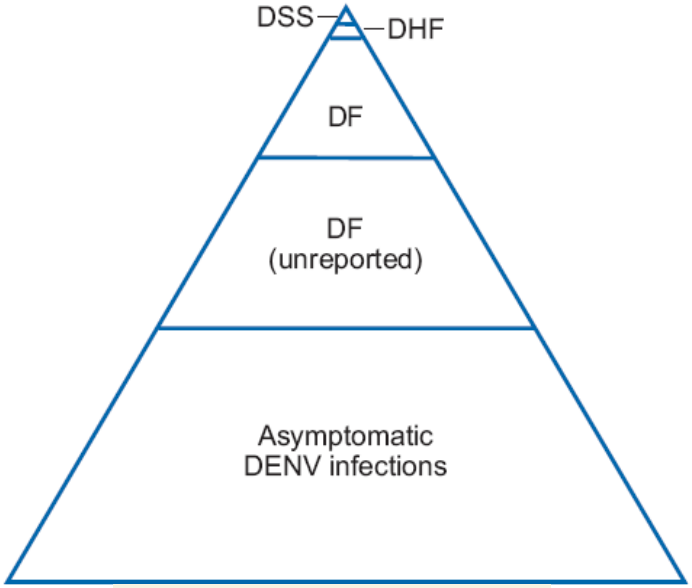
Seroprevalence of DENV Exposure in USASOC Personnel

- USASOC and WRAIR viral disease threat characterization
- Pre- and post-deployment sample collection in deploying SOC personnel
- Tested for presence of neutralizing antibody by microneut assay

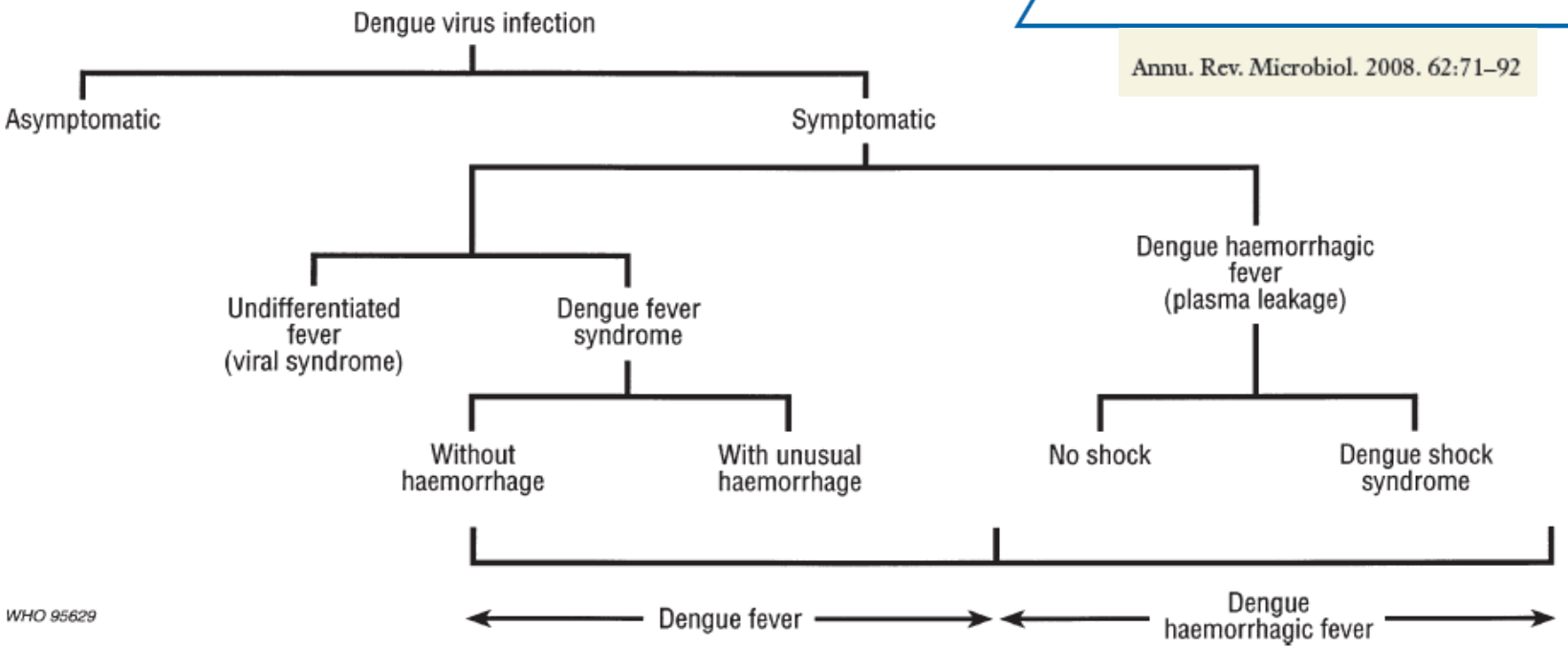
- As of AUG 2013 360 samples tested
  - N = 47 positive samples (13.0%)
  - N = 9 positive samples (2.5%) with monovalent profile

- **Summary: USASOC personnel are highly primed to dengue, a proportion are in high risk category for severe disease with secondary infection, clinical impact will likely not be documented, is this knowledge changing approach to febrile patient during deployment?**

Dengue Infection Clinical Phenotypes



Annu. Rev. Microbiol. 2008. 62:71–92



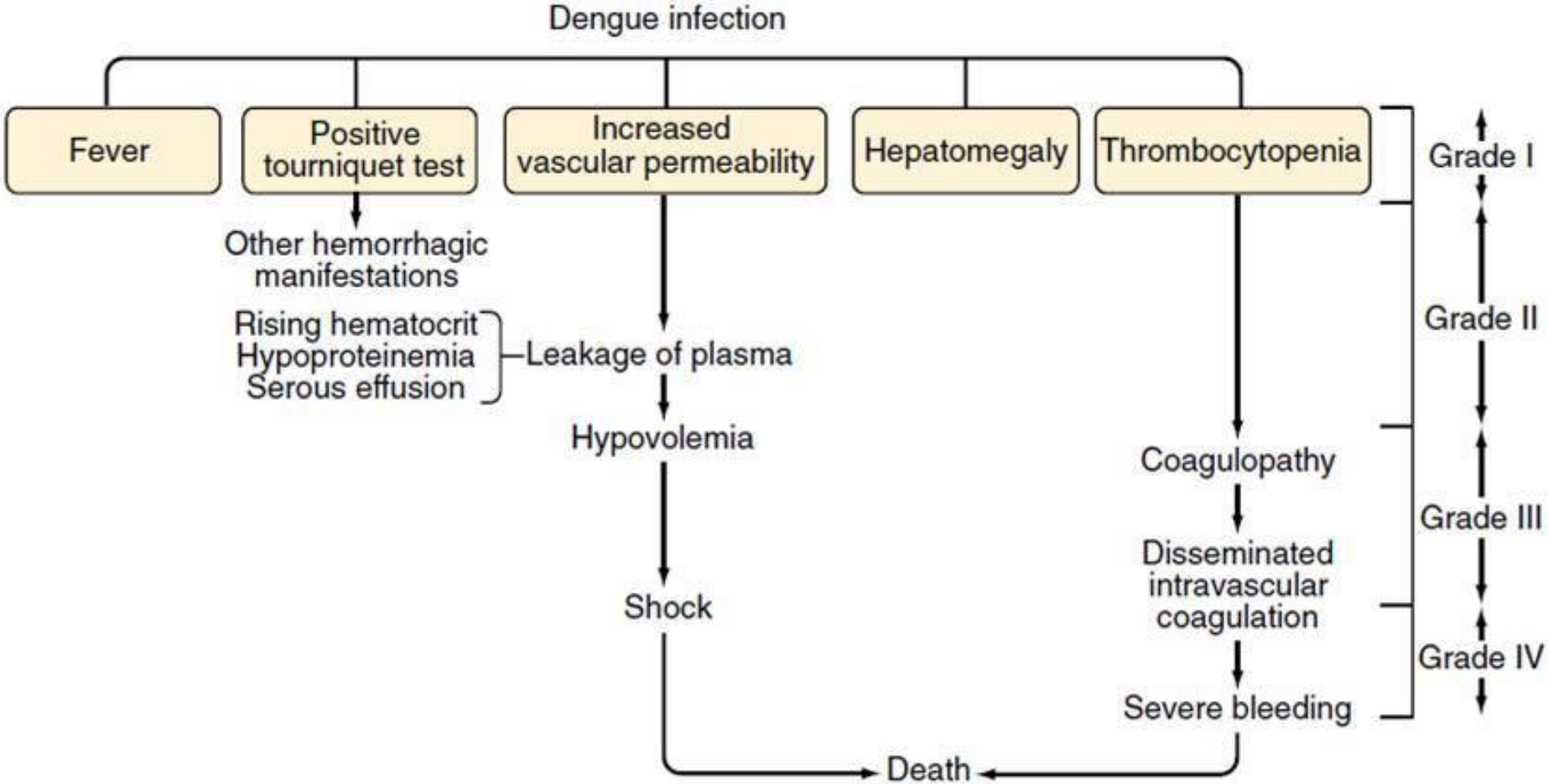


Figure 153-5 Clinical spectrum, pathophysiology, and classification of dengue hemorrhagic fever. At the top are key clinical findings; in the center, pathophysiologic mechanisms; and on the side, the World Health Organization classification of cases: *Grade 1:* Fever accompanied by nonspecific constitutional symptoms; the only hemorrhagic manifestations are a positive tourniquet test result, easy bruising, or both. *Grade 2:* Spontaneous bleeding in addition to the manifestations of grade 1, usually in the form of skin hemorrhages or other hemorrhages. *Grade 3:* Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin and restlessness. *Grade 4:* Profound shock with undetectable blood pressure or pulse. *(From World Health Organization.* Technical Guide for Diagnosis, Treatment, Surveillance, Prevention, and Control of Dengue Haemorrhagic Fever, *2nd ed. Geneva: World Health Organization; 1997.)*

Dengue Hemorrhagic Fever

Table 1. WHO Classification of DHF

Grades	Increase in Hematocrit*	Hemorrhage†	Shock‡	Profound shock§
1	+	−	−	−
2	+	+	−	−
3	+	±	+	−
4	+	±	+	+

*Hematocrit increased by at least 20%.
†Spontaneous bleeding in skin and/or other sites.
‡Hypotension and/or narrowing of pulse pressure to 20 mmHg or less, with cold clammy skin and restlessness.
§Undetectable blood pressure or pulse.

Dengue haemorrhagic fever

Diagnosis, treatment, prevention and control

SECOND EDITION

World Health Organization
Geneva
1997

DENGUE

GUIDELINES FOR DIAGNOSIS, TREATMENT, PREVENTION AND CONTROL

New edition
2009

TDR For research on diseases of poverty
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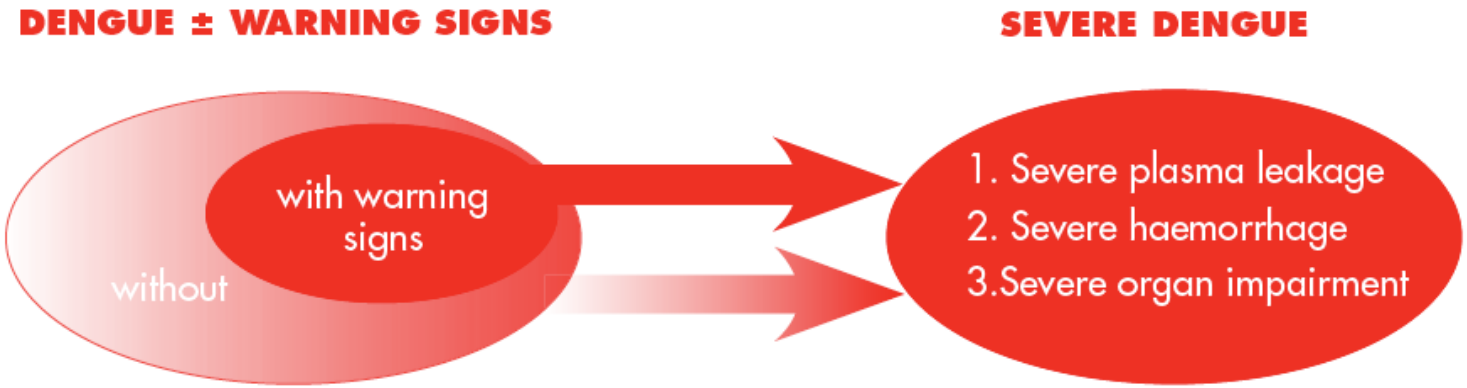
World Health Organization

Figure 1.4 Suggested dengue case classification and levels of severity



CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

live in /travel to dengue endemic area.
Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue

(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

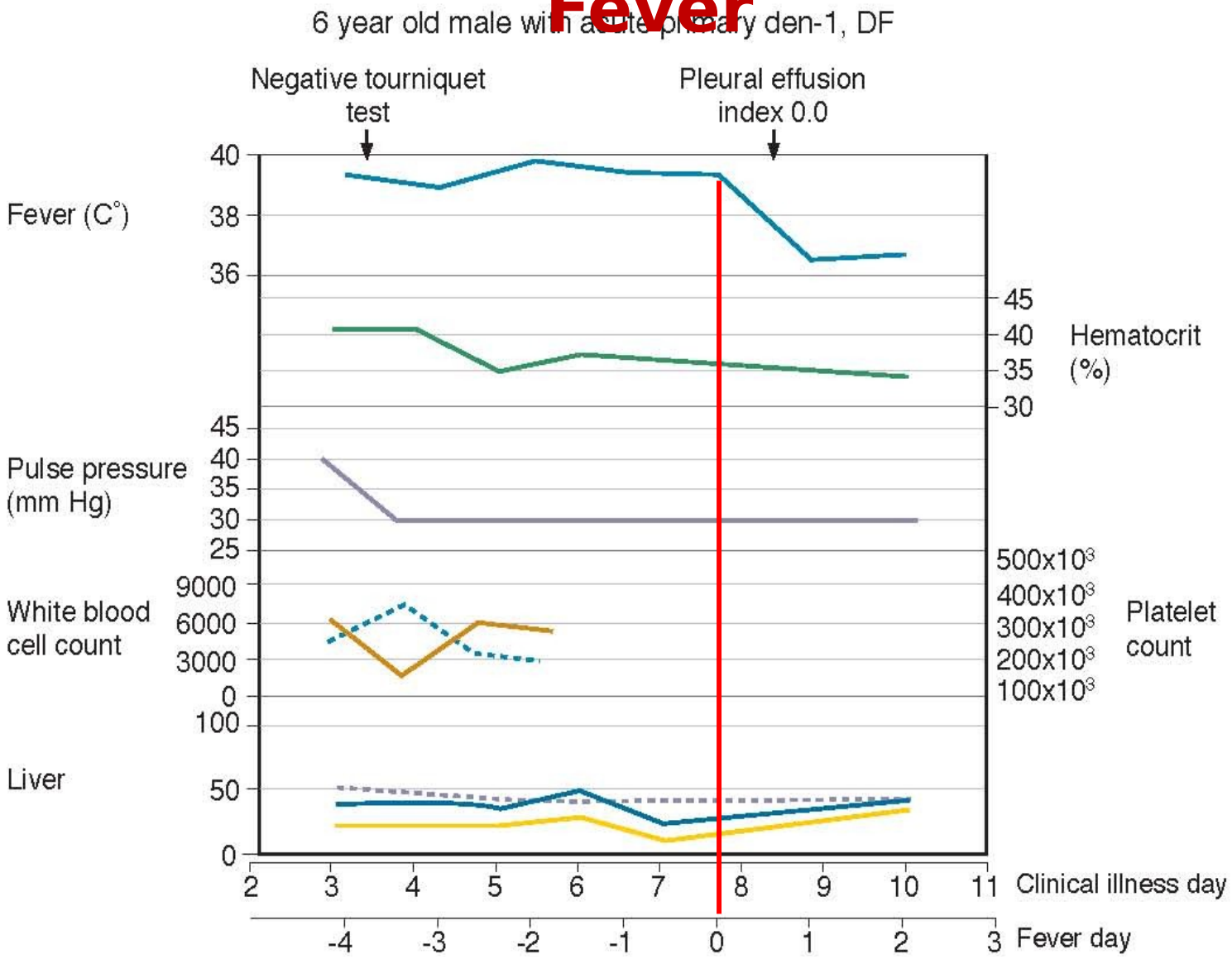
Severe bleeding

as evaluated by clinician

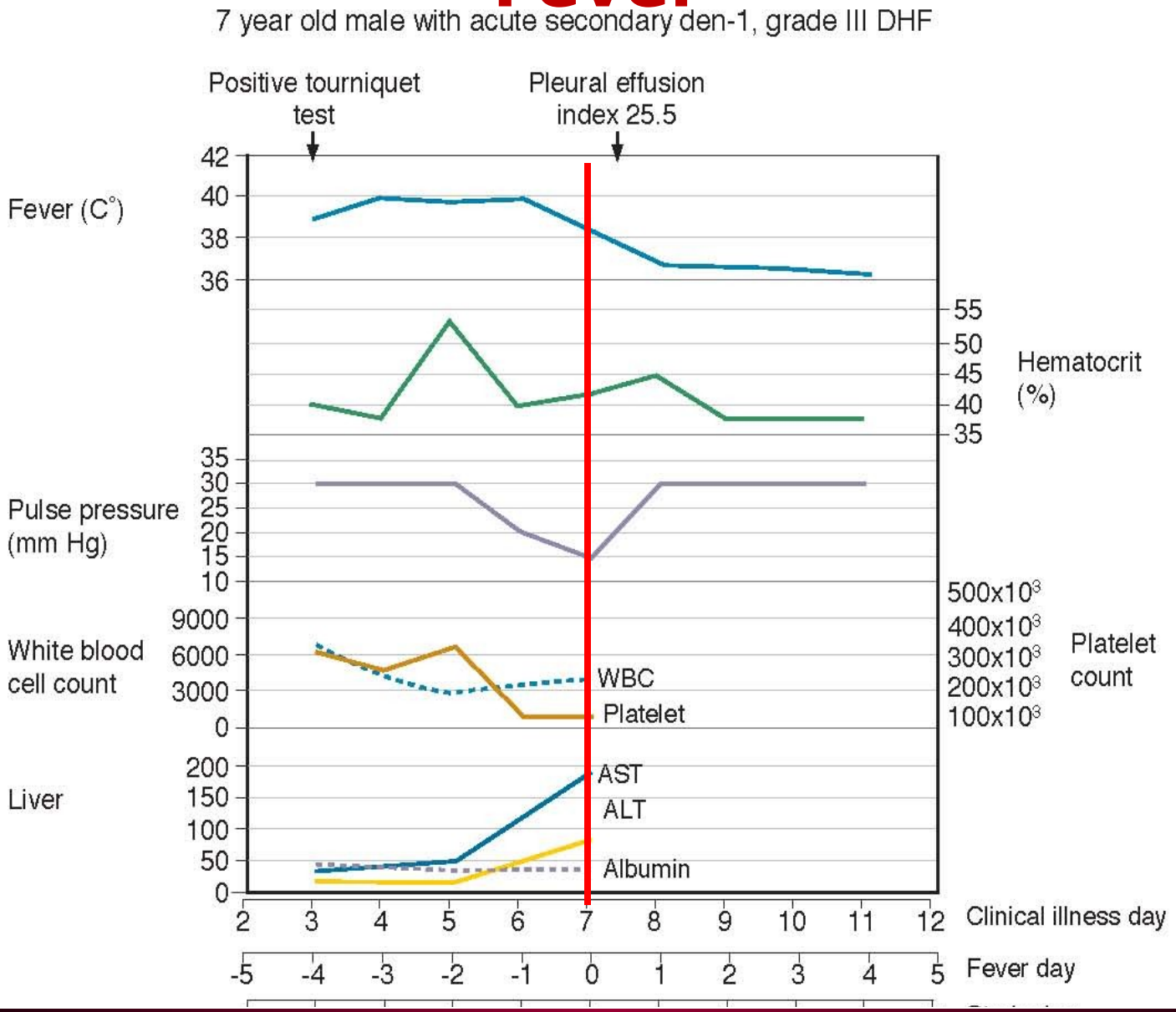
Severe organ involvement

- Liver: AST or ALT >=1000
- CNS: Impaired consciousness
- Heart and other organs

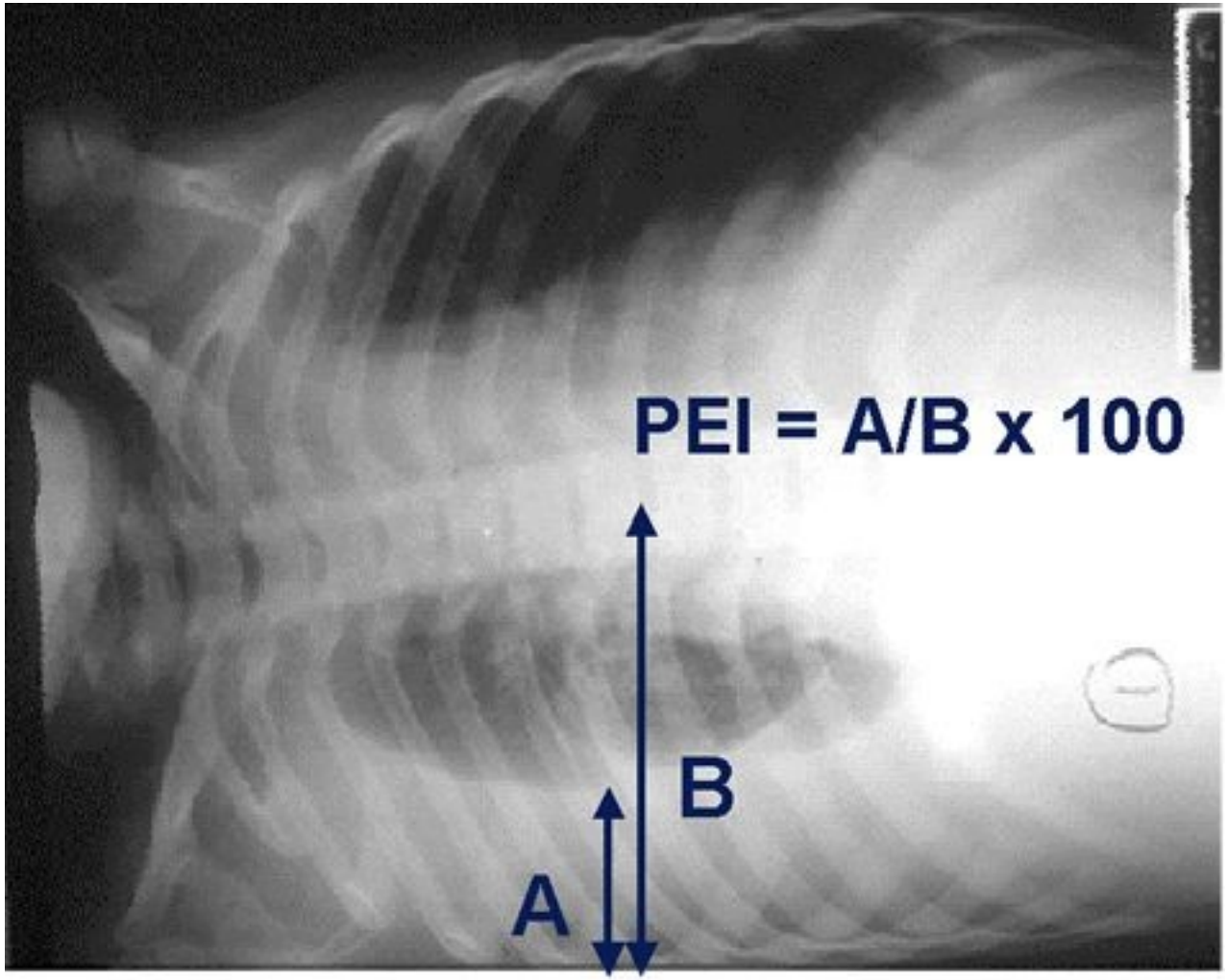
Dengue Fever



Dengue Hemorrhagic Fever

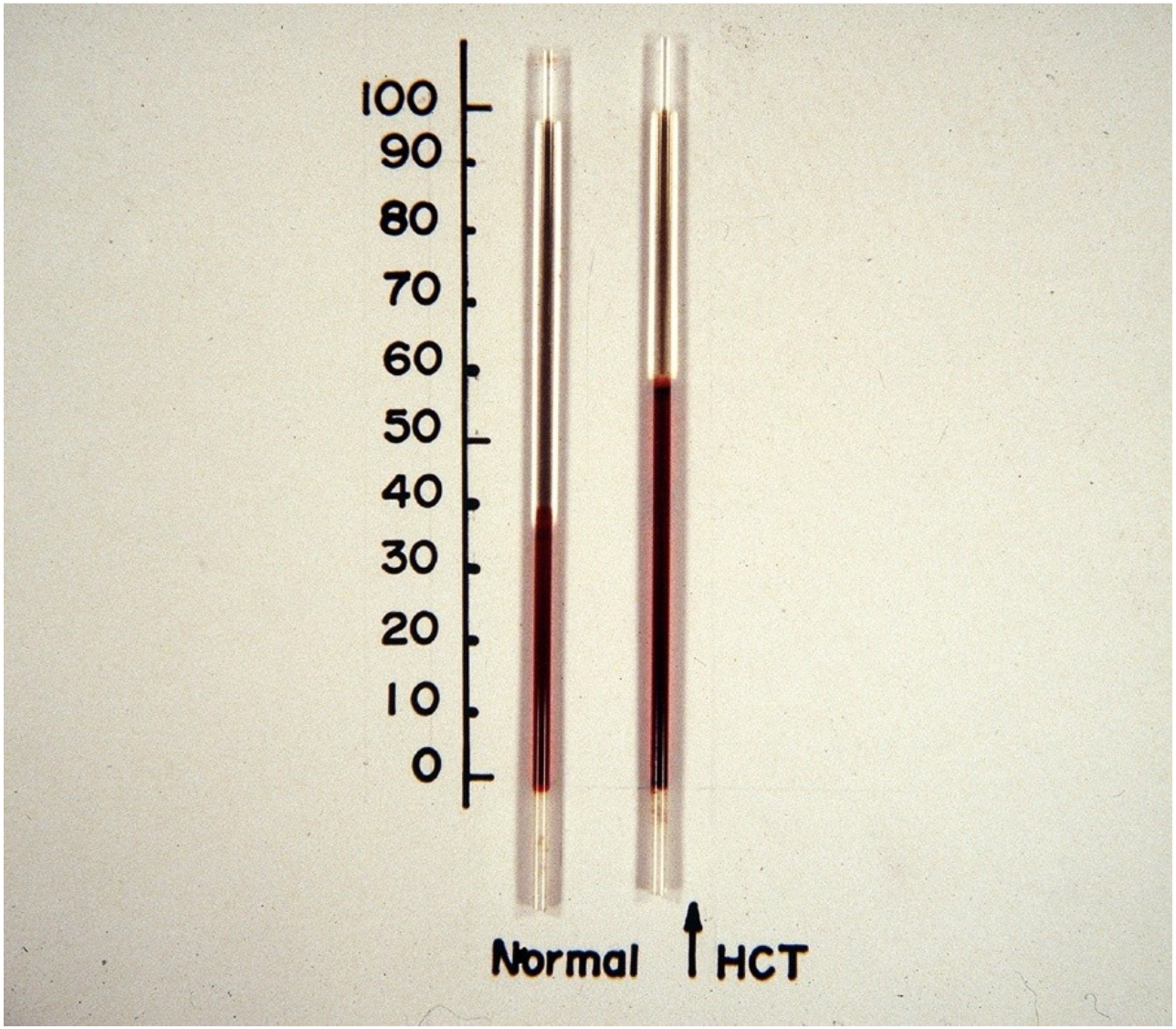


Pleural Effusion Index



R LAT decubitus X-ray showing a large pleural effusion, DHF the day after defervescence. Degree of plasma leakage may be quantified by means of the pleural effusion index. The pleural effusion index is calculated as 100 times the maximum width of the R pleural effusion, divided by the maximal width of the R hemithorax.

Hemoconcentration

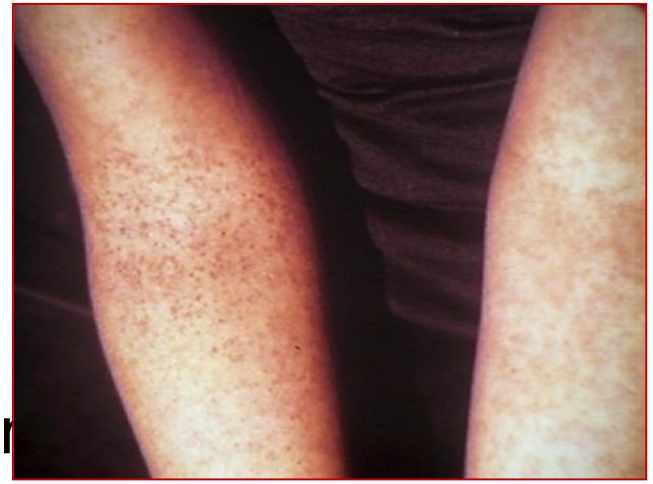


Diagnosing Dengue

- Maintain high degree of suspicion
  - Geographic location
  - Clustering of cases
- History and physical
  - Clinical presentation
  - Vital signs (HR, BP, Temp)
  - Dengue tourniquet test (TT)
- Clinical lab assessment
  - CBC (WBC, HCT, PLT), AST/ALT
- Dengue area, +Clinical, +TT, WBC<5k = High PPV

Dengue Tourniquet Test

- Measure BP
- SBP + DBP / 2 = target insufflation pressure for test
- Inspect area near antecubital fossa
  - You will assess delta before / after
- Inflate to target pressure
- Hold for 5 minutes
- Remove cuff
- Reassess antecubital fossa
- Count # of petechiae in 2.5 cm^2 ar
- ≥10 new petechiae is positive



Evaluation of diagnostic tests: dengue

UNICEF • UNDP • World Bank • WHO

Rosanna W. Peeling, Harvey Artsob, Jose Luis Pelegrino, Philippe Buchy, Mary J. Cardosa, Shamala Devi, Delia A. Enria, Jeremy Farrar, Duane J. Gubler, Maria G. Guzman, Scott B. Halstead, Elizabeth Hunsperger, Susie Kliks, Harold S. Margolis, Carl M. Nathanson, Vinh Chau Nguyen, Nidia Rizzo, Susana Vázquez and Sutee Yoksan

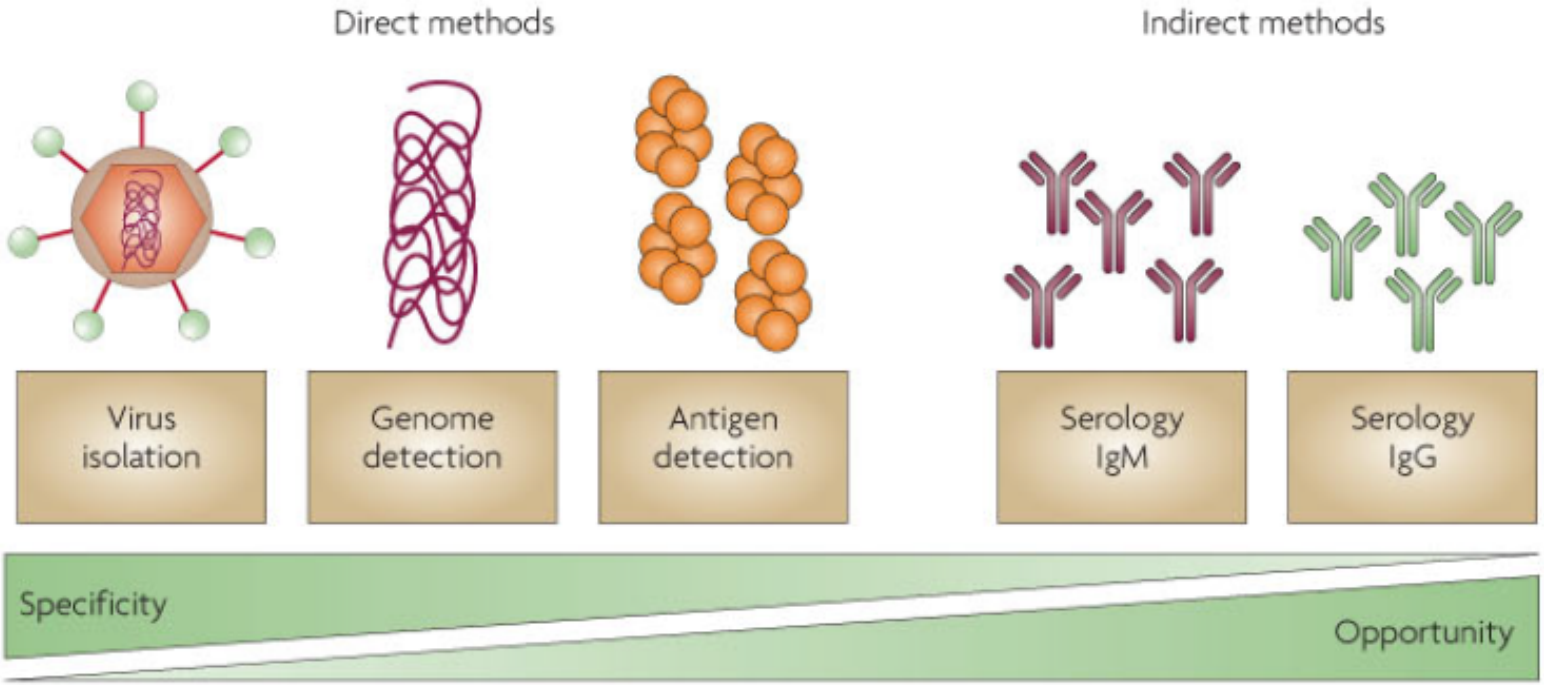
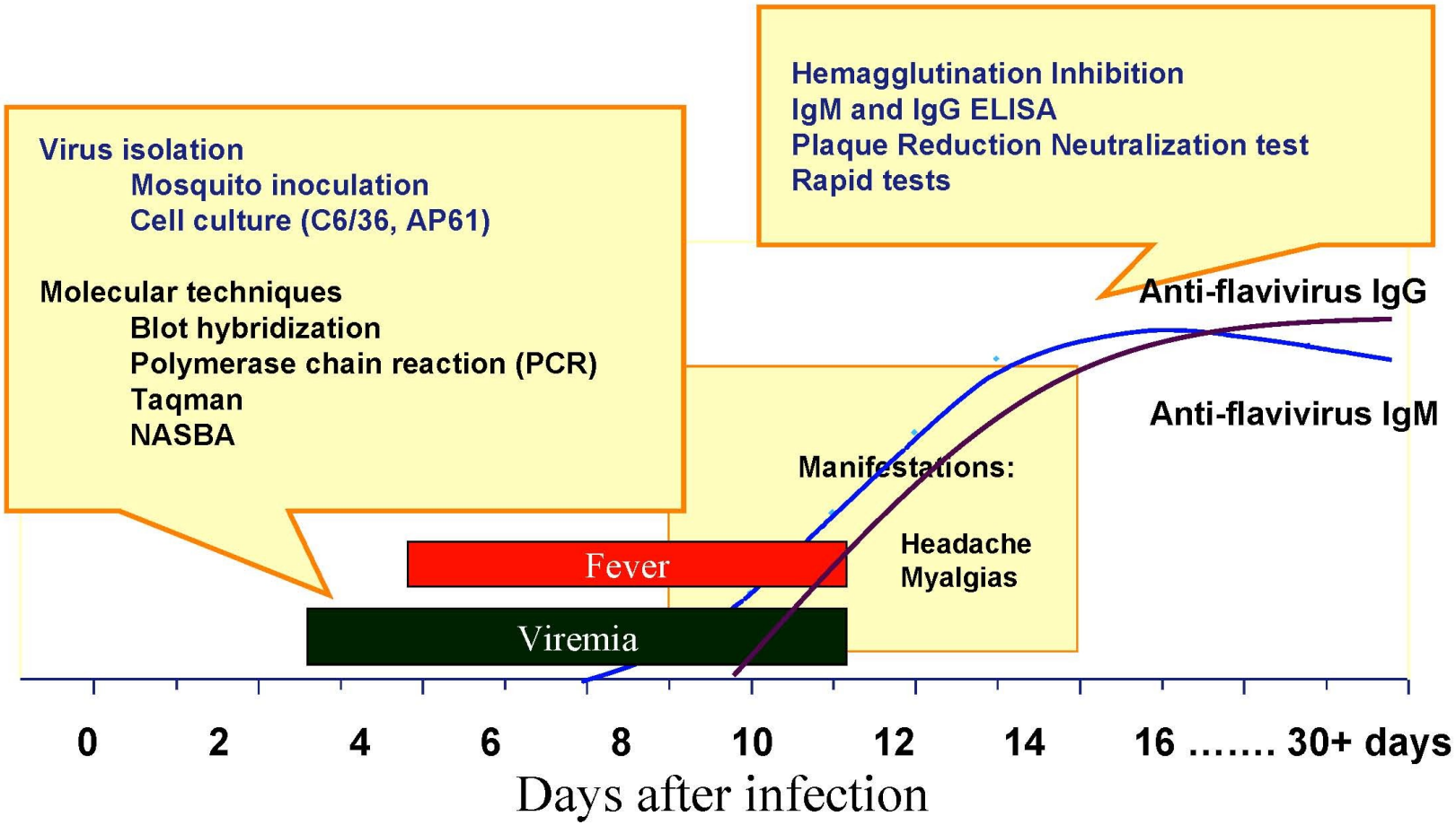


Figure 1 | **Comparative merits of direct and indirect laboratory methods for the diagnosis of dengue infections.** Opportunity refers to the fact that antibody testing is usually the most practical diagnostic option available.

Disease – Windows of Diagnostic Opportunity



Dengue

N Engl J Med 2012;366:1423-32.

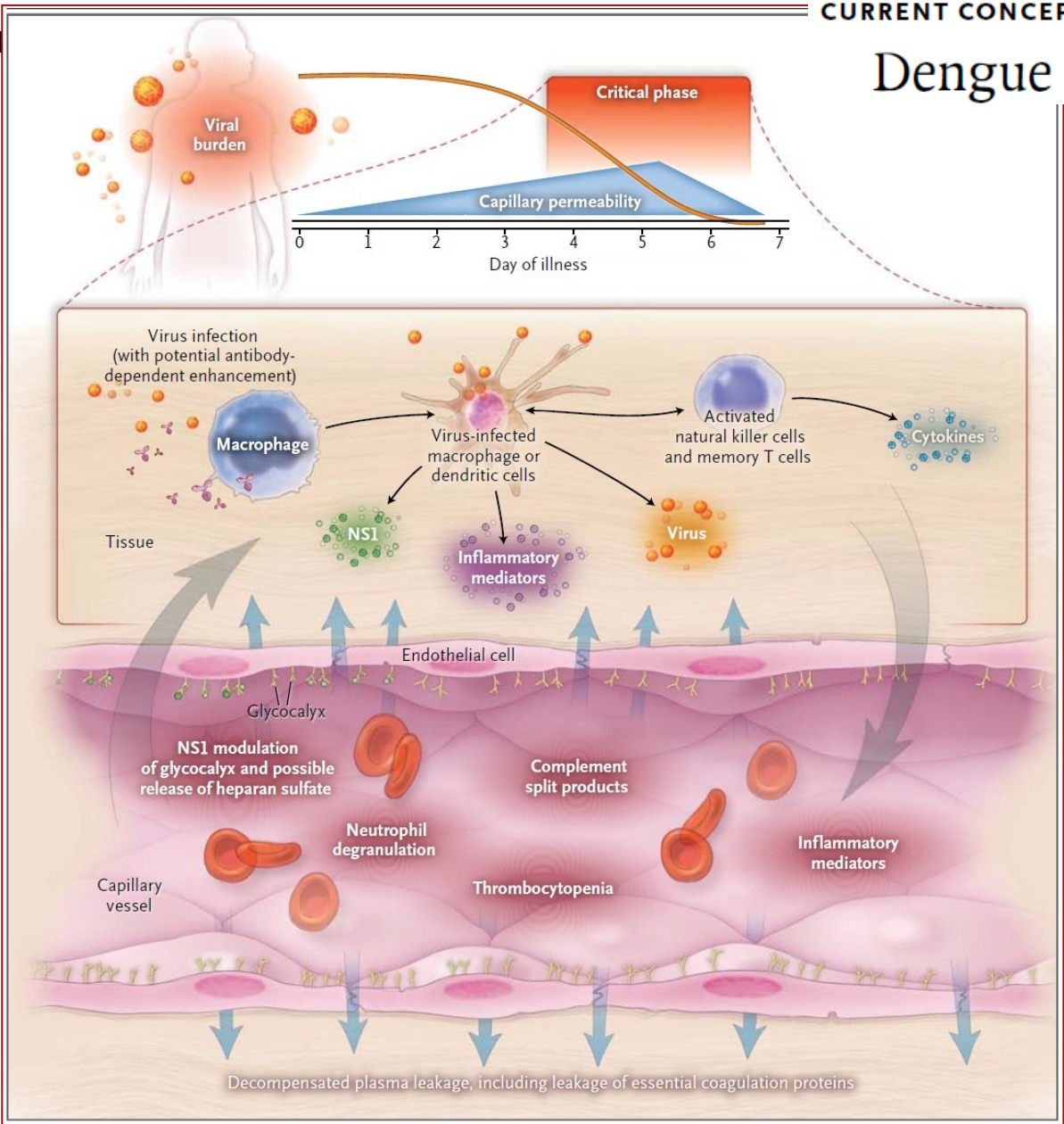


Figure 2 (facing page). Immunopathogenesis of Severe Dengue in Secondary Infections.

The kinetics of viremia in a patient with secondary dengue, the timing of common complications, and possible mechanistic causes are shown. Early in secondary infection (or primary infection of infants), antibody-dependent enhancement is thought to increase in vivo concentrations of virus.[17] Antibody-dependent enhancement is linked to the presence of non-neutralizing or subneutralizing levels of dengue virus–reactive IgG induced by a primary infection, or acquired passively in newborns. A large infected cell mass results in elevated concentrations of acute-phase response proteins, cytokines, and chemokines; generation of immune complexes; and consumption of complement and release of split products. The activation, proliferation, and secretion of cytokines in tissues by memory T lymphocytes recognizing conserved and altered peptide ligands are postulated to add to the inflammatory milieu during secondary infections. Collectively, the host immunologic response is thought to create a physiological environment in tissues that promotes capillary permeability when the viral burden is in rapid decline. However, the exact mechanisms are unclear. Interactions between dengue nonstructural protein 1 (NS1) and the surface glycocalyx layer may result in release of heparan sulfate into the circulation, thereby altering the filtration characteristics of the layer and resulting in leakage of proteins. Loss of essential coagulation proteins probably plays a major role in the development of the typical coagulopathy, which is usually manifested as an increase in the partial-thromboplastin time accompanied by low fibrinogen levels but with little evidence of procoagulant activation. Heparan sulfate may also function as an anticoagulant and contribute to the coagulopathy.

Dengue Treatment

DENGUE WITHOUT WARNING SIGNS

Group A
(May be sent home)

Group criteria

Patients who do not have warning signs
AND
who are able:

- to tolerate adequate volumes of oral fluids
- to pass urine at least once every 6 hours

Laboratory tests

- full blood count (FBC)
- haematocrit (HCT)

Treatment

Advice for:

- adequate bed rest
- adequate fluid intake
- Paracetamol, 4 gram maximum per day in adults and accordingly in children.

Patients with stable HCT can be sent home.

Monitoring

Daily review for disease progression:

- decreasing white blood cell count
- defervescence
- warning signs (until out of critical period).

Advice for immediate return to hospital if development of any warning signs, and

- written advice for management (e.g. home care card for dengue).

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DENGUE WITH WARNING SIGNS

Group B

(Referred for in-hospital care)

Group criteria

Patients with any of the following features:

- co-existing conditions such as pregnancy, infancy, old age, diabetes mellitus, renal failure
- social circumstances such as living alone, living far from hospital

Laboratory tests

- full blood count (FBC)
- haematocrit (HCT)

Treatment

- Encouragement for oral fluids. If not tolerated, start intravenous fluid therapy 0,9% saline or Ringer's Lactate at maintenance rate.

Monitoring

Monitor:

- temperature pattern
- volume of fluid intake and losses
- urine output (volume and frequency)
- warning signs
- HCT, white blood cell and platelet counts.

Figure 2.2 Algorithm for fluid management in compensated shock

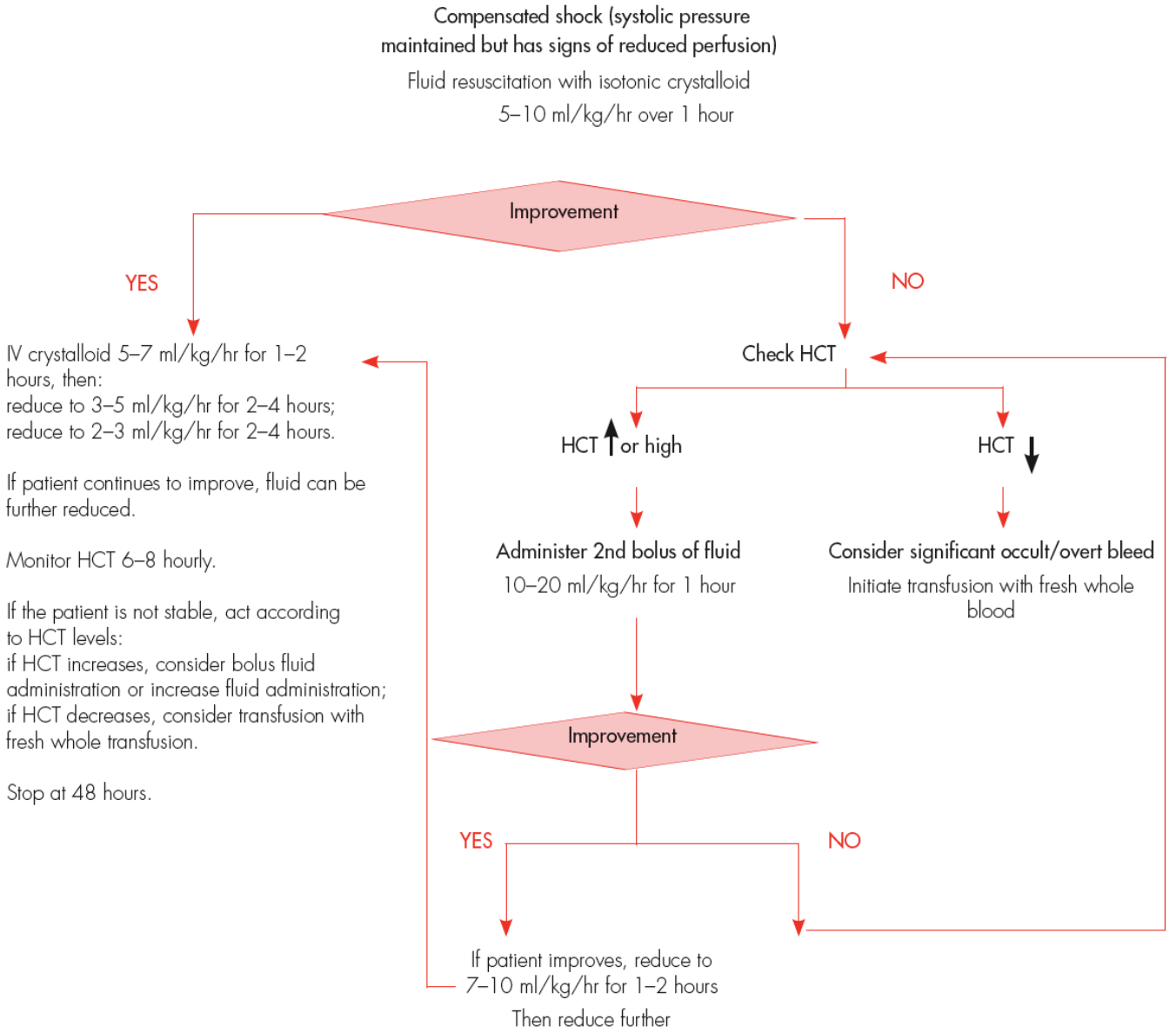
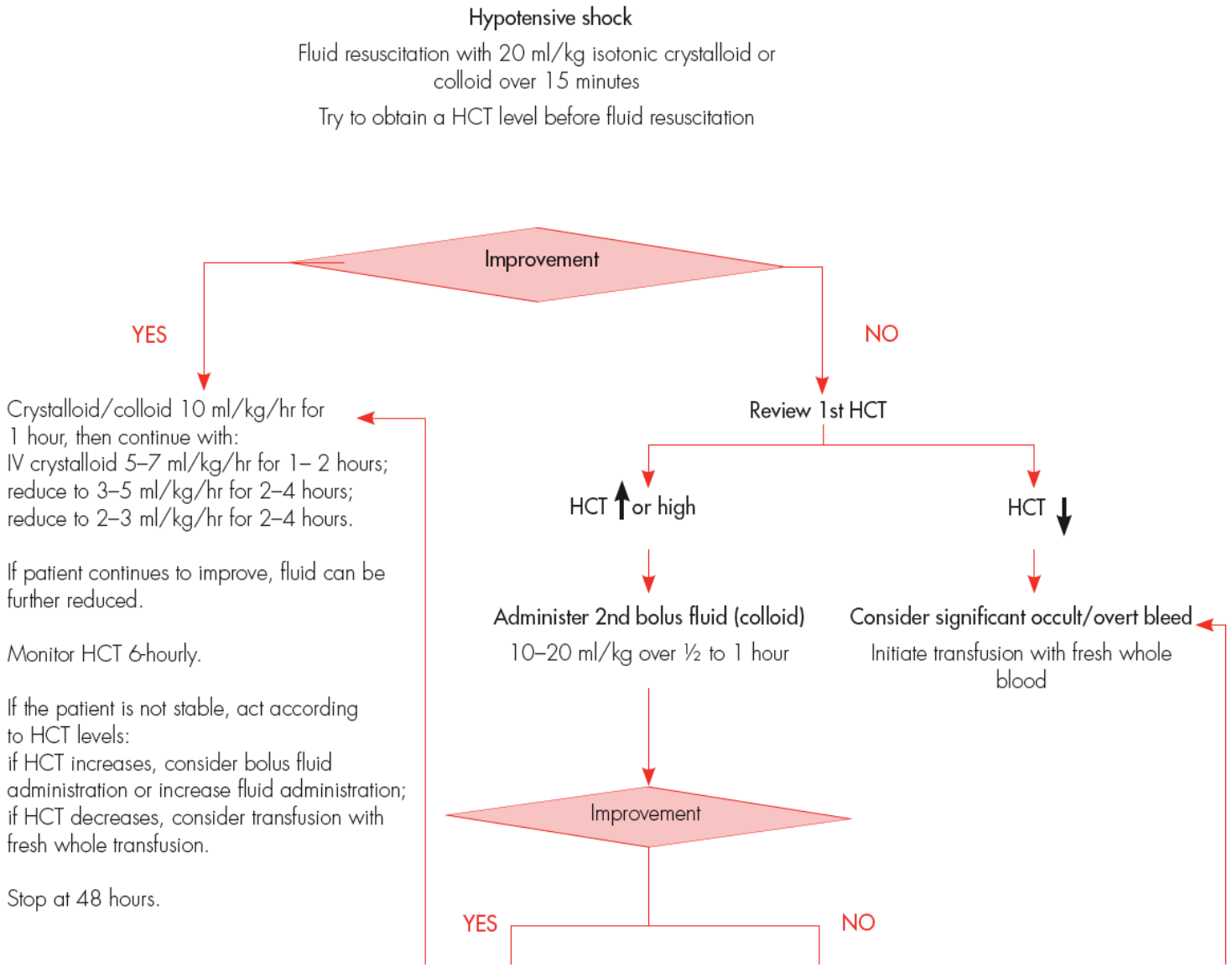
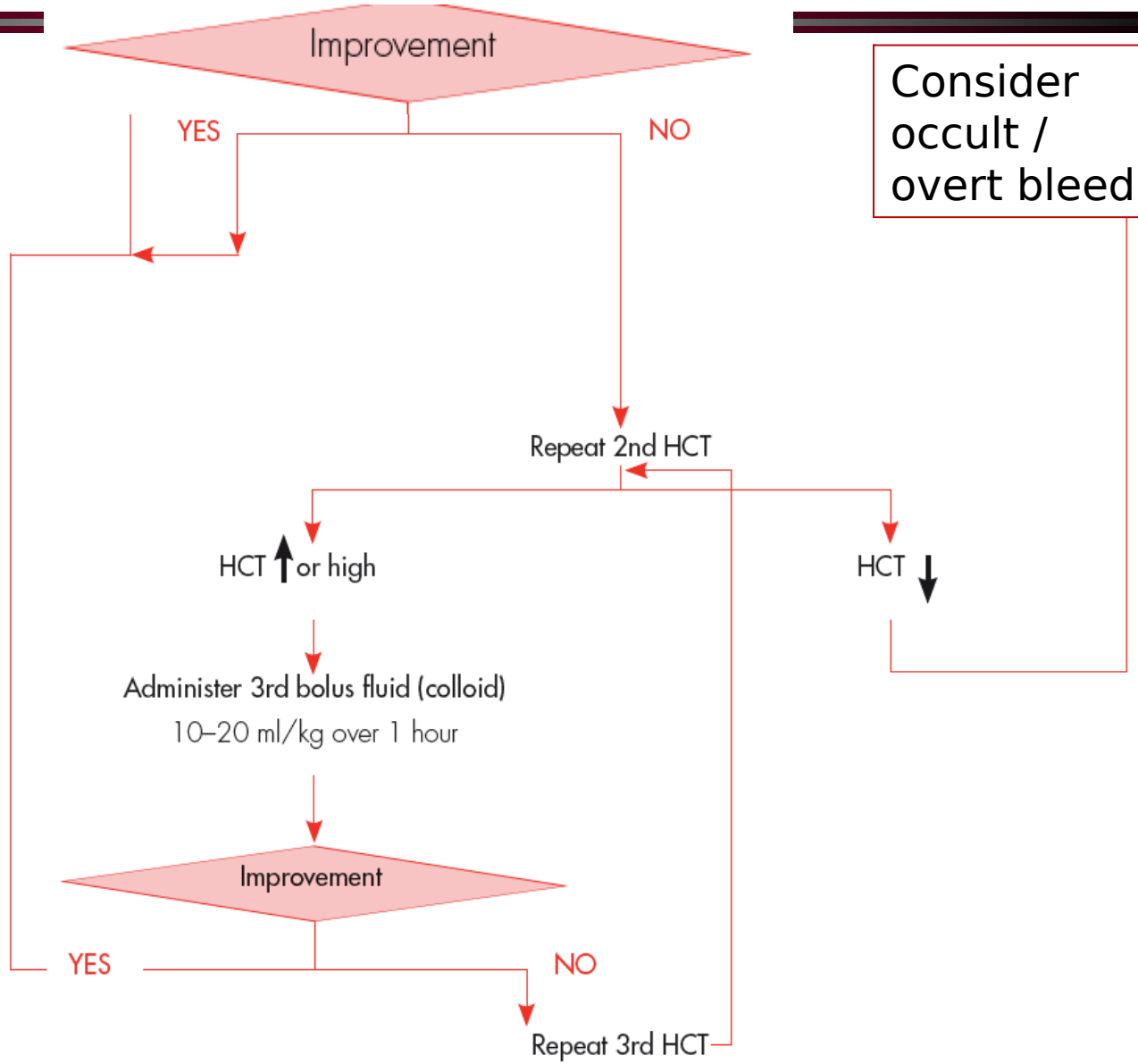


Figure 2.3 Algorithm for fluid management in hypotensive shock




Improvement
YES
NO
Consider occult / overt bleed
Repeat 2nd HCT
HCT ↑ or high
HCT ↓
Administer 3rd bolus fluid (colloid)
10–20 ml/kg over 1 hour
Improvement
YES
NO
Repeat 3rd HCT

	Good practice	Bad practice
1	Assessment and follow-up of patients with non-severe dengue and careful instruction of warning signs to watch out for	Sending patients with non-severe dengue home with no follow-up and inadequate instructions
2	Administration of paracetamol for high fever if the patient is uncomfortable	Administration of acetylsalicylic acid (aspirin) or ibuprofen
3	Obtaining a haematocrit level before and after fluid boluses	Not knowing when haematocrit levels are taken with respect to fluid therapy
4	Clinical assessment of the haemodynamic status before and after each fluid bolus	No clinical assessment of patient with respect to fluid therapy
5	Interpretation of haematocrit levels in the context of fluid administered and haemodynamic assessment	Interpretation of haematocrit levels independent of clinical status
6	Administration of intravenous fluids for repeated vomiting or a high or rapidly rising haematocrit	Administration of intravenous fluids to any patient with non-severe dengue
7	Use of isotonic intravenous fluids for severe dengue	Use of hypotonic intravenous fluids for severe dengue
8	Giving intravenous fluid volume just sufficient to maintain effective circulation during the period of plasma leakage for severe dengue	Excessive or prolonged intravenous fluid administration for severe dengue
9	Avoiding intramuscular injections in dengue patients	Giving intramuscular injections to dengue patients
10	Intravenous fluid rate and frequency of monitoring and haematocrit measurement adjusted according to the patient's condition	Fixed intravenous fluid rate and unchanged frequency of monitoring and haematocrit measurement during entire hospitalization for severe dengue
11	Close monitoring of blood glucose, i.e. tight glycaemic control	Not monitoring blood glucose, unaware of the hyperglycaemic effect on osmotic diuresis and confounding hypovolaemia
12	Discontinuation or reducing fluid therapy once haemodynamic status stabilizes	Continuation and no review of intravenous fluid therapy once haemodynamic status stabilizes

Questions.